ISSN 0003-2999
Volume 71, Number 5, November 1990

Anesthesia and Analgesia

35

VOL - 72
5-6
1990

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

P, 24,554

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

cuk-H02981-35-P024554

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with tropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal an be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also e used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
µg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

References:

1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983;58:438-440.
2. Lowry KG, Mirakhur RK, Lavery GG, et al: Vecuronium and atracurium in the elderly: A clinical comparison with pancuronium. *Acta Anaesthesiol Scand* 1985;29:405-408.
3. Miller RD, Rupp SM, Fahey MR, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron*. Amsterdam, Excerpta Medica, 1983, pp 124-126.
4. Bell CF, Hunter JM, Jones RS, et al: Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985;57:160-168.

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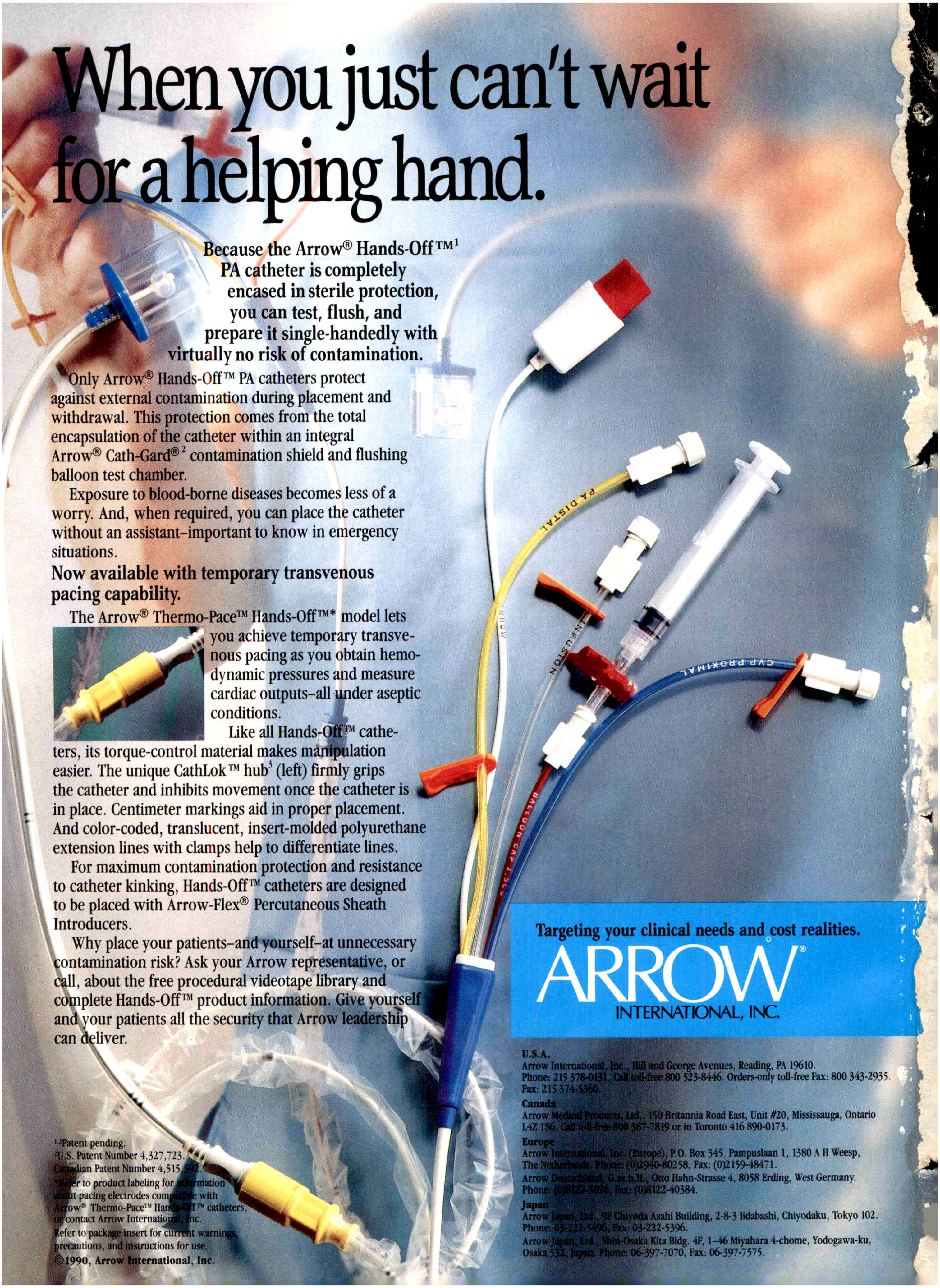

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[1,3] Patent pending.

[2] U.S. Patent Number 4,327,723.
Canadian Patent Number 4,515,592.

*Refer to product labeling for information about pacing electrodes compatible with Arrow® Thermo-Pace™ Hands-Off™ catheters, or contact Arrow International, Inc.

Refer to package insert for current warnings, precautions, and instructions for use.

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Anesthesia and Analgesia

Journal of International Anesthesia Research Society

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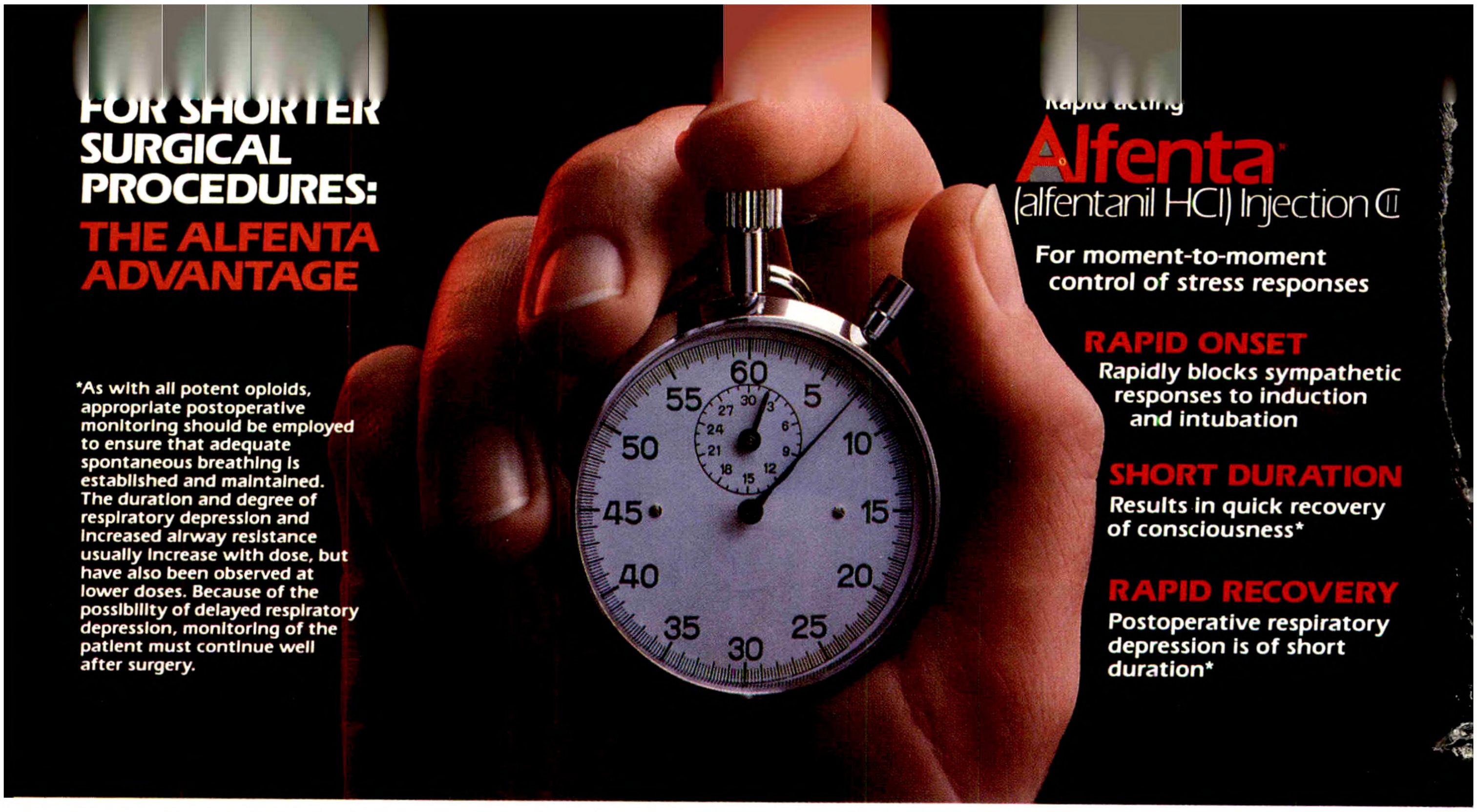

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SHORT DURATION

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RAPID RECOVERY

Postoperative respiratory depression is of short duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

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DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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March 1987, April 1988
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49-7619902-M

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Anesthesia and Analgesia

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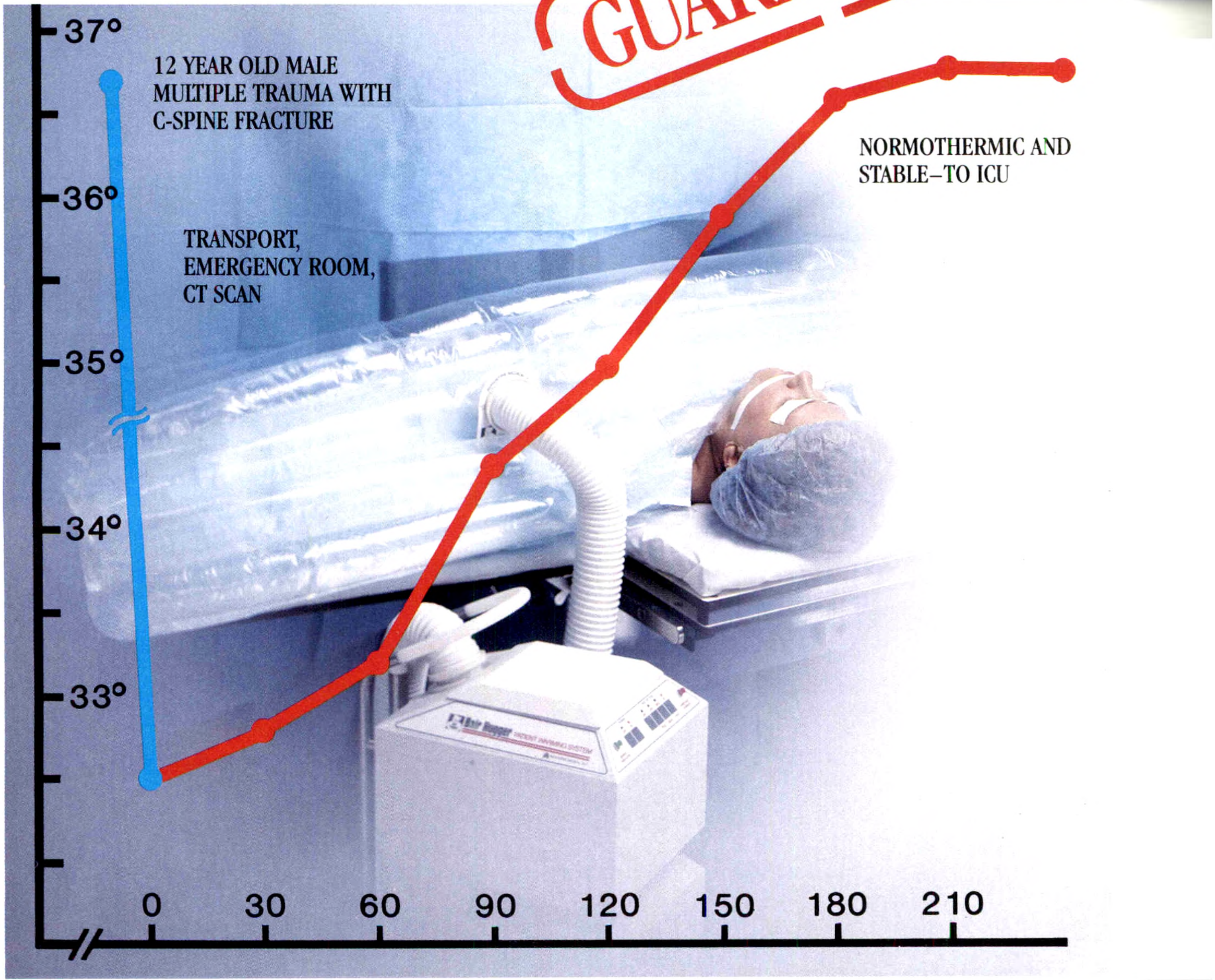

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IARS

NEW OFFICE ADDRESS

Effective October 1, 1990, the **International Anesthesia Research Society** headquarters office in Cleveland moved to the following new address:

International Anesthesia
Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

NEW TELEPHONE NUMBER:
(216) 642-1124

All membership payments and correspondence regarding **IARS** member subscriptions, annual scientific meeting matters, the B.B. Sankey Anesthesia Advancement Award, etc., should be sent to the above address.

The **American Board of Anesthesiology (ABA)** will administer its fourth written examination in **CRITICAL CARE MEDICINE** at the Westin Hotel-O'Hare in Rosemont, Illinois on Friday, September 27, 1991. Diplomates of the ABA and other ABMS Member Boards who apply and are judged to be qualified by virtue of their additional training or experience in Critical Care Medicine will be accepted for examination. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 100 Constitution Plaza, Hartford, Connecticut 06103-1721. The deadline for receipt of completed applications in the Board office is April 30, 1991.

1991 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1991 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **December 14, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

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The 1991 Award(s) will be announced at the Annual Scientific Meeting (65th Congress) of the International Anesthesia Research Society to be held at the Marriott Rivercenter, San Antonio, Texas, March 8–12, 1991.

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Mock Orals Help Dr. Smith

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The *Osler Institute* Anesthesiology Oral Boards Tutorial

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Dear Fellow Physician:

Dr. Smith (not his real name) had failed his oral boards several times. His group was satisfied with his work but his job depended on becoming board certified. He was eligible to take the exam only one more time. A friend advised him to take our Osler Institute's Anesthesiology Board Review Course.

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Great Lectures

At the course, Dr. Smith enjoyed six days of outstanding lectures by some of the best-known teachers in anesthesiology – as well as by several outstanding junior faculty who had been asked back because of their excellent participant evaluation scores. Also several new faculty had been recommended for their speaking ability.

Some of the lectures were of little use to Dr. Smith – he is regarded as an expert in his field; he could have given several of the lectures himself. Knowledge was not his problem; his problem was presenting his knowledge in the oral exam. He skipped several lectures to attend:

Mock Oral Exams

The first day of the course, a recently retired board examiner explained the philosophy, process, and scoring of the real oral exam. Each evening as well as concurrent with most lectures there were mock oral exams for Dr. Smith. These are group sessions with one participant taking the hot seat for about 25 minutes while others watch. Each participant is entitled to a turn in the hot seat as well as unlimited observation of others.

When Dr. Smith took the hot seat his heart quickened, his palms sweated, and his hands shook. The faculty presented a stem question, paused a minute, then asked the first question. Dr. Smith opened his mouth, but his tongue was thick and dry. He stammered and stuttered – failed to form even a sentence – just like when he failed the real oral exam. But this time was different; the faculty coached and encouraged him. His panic passed and his performance improved.

Extra Mock Orals

The course budget could not support enough faculty for an unlimited number of mock orals for every participant. In our previous course, assertive attendees had taken the hot seat repeatedly before others had a chance. In response, we mark participant name tags for the first mock oral. We also hire additional faculty time and sell $70 tickets for extra turns in the hot seat.

Dr. Smith became more comfortable in the hot seat. He continued to improve.

Private and Dual Orals

Dr. Lee, however, was too shy to take the hot seat in front of anyone else. We now have a thirty dollar surcharge for private sessions. Also, Dr. Jones wanted two examiners, just like the real exam. Such sessions take twice the faculty time, so we must charge $140 per session.

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At our June course, we had a portable TV studio to make educational tapes with some of the faculty. Video taping mock orals was so popular that we now offer a video tape of your practice exam for an extra thirty dollars per session.

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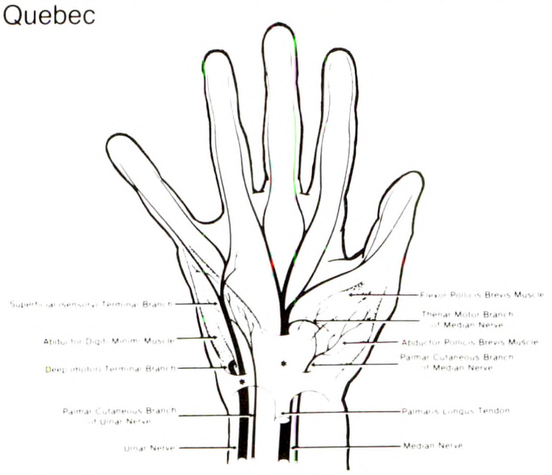
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Ulnar Nerve
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Thenar Motor Branch of Median Nerve
Abductor Pollicis Brevis Muscle
Palmar Cutaneous Branch of Median Nerve
Palmaris Longus Tendon
Median Nerve

FIGURE 12.1 Palmar view of the right wrist and hand, showing the course and branching of the median and ulnar nerves. These nerves first divide into the common digital nerves, which then divide further to become individual proper palmar digital nerves. The transverse carpal ligament and its extension, which forms the roof of Guyon's canal, are marked with asterisks.

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2 Pathological Process Producing Focal Peripheral Neuropathies
3 Electrical Activity in Normal and Abnormal Nerves
4 The Evaluation of Patients with Focal Neuropathies
5 The Cervical Spinal Nerve Roots and Spinal Nerves
6 The Cervical Plexus and the Nerves of the Neck
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8 The Nerves Arising from the Brachial Plexus
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18 The Femoral and Saphenous Nerves
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MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in December to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the **NEW IARS OFFICE ADDRESS:** Suite 140, 2 Summit Park Drive, Cleveland, OH 44131. Tel: (216) 642-1124.

MEETING SCHEDULE: **Registration:** Friday, March 8, 1–6 PM
Scientific Program: Saturday–Tuesday, March 12
Exhibits: Saturday–Monday, March 11

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture, Sunday, March 10, ***"Anesthesiology and its Journals"***
Nicholas M. Greene, MD, Emeritus Professor of Anesthesiology,
Yale University School of Medicine, New Haven, Connecticut,
and Editor-in-Chief, *ANESTHESIA and ANALGESIA*

REVIEW COURSE LECTURES:

MD Abel, MD — Transesophageal Echocardiography — Its Real Role in Clinical Anesthesia
PG Barash, MD — Preoperative Assessment of the Patient With Cardiac Disease
DR Bevan, MD, and RD Miller, MD — Anesthesia Literature — A Critical Approach to Reading and Writing
DR Cook, MD — Anesthetic Management of Neonatal and Infant Surgical Emergencies
MJ Cousins, MD — The Injury Response and the Prevention of Postoperative Pain
BG Covino, MD — New Techniques in Regional Anesthesia
N Ellison, MD — Blood Transfusions — When and What?
M Finster, MD — New Trends in Obstetric Pain Relief
AB Froese, MD — Ventilator-Related Lung Injury — New Concepts
TJ Gal, MD — Anesthesia and Gas Exchange — HPV, FRC, CC, and Other Acronyms
DE Longnecker, MD — The Case for Perioperative Blood Pressure Control
M Maze, MD — Alpha-2 Agonists and Anesthesia
SC Nicolson, MD — Perioperative Fluid Management in the Pediatric Patient
WS Nimmo, MD — Alternate Modes of Drug Delivery
GW Ostheimer, MD — Contemporary Issues in Obstetric Anesthesia
RG Pearl, MD — Sepsis — Etiology and Management
DS Prough, MD — Anesthetic Management of the Patient With Head Trauma
C Prys-Roberts, DM — Total Intravenous Anesthesia — Assessment of Adequacy
JG Reves, MD — Physiology of Cardiopulmonary Bypass
JJ Savarese, MD — Does the Choice of Muscle Relaxant Really Matter?
S Slogoff, MD — Outcome Studies in Anesthetic Data — A Perspective
NT Smith, MD — Perioperative Anesthetic Data — What to Do With It?
RK Stoelting, MD — Allergy and Anesthesia
JH Tinker, MD — How?/Should?/Does? Malpractice Litigation Affect Anesthetic Practice?
PF White, MD — Monitored Anesthesia Care — Appropriate Use of Adjuvant Drugs
MP Yeager, MD — The Role of Regional Anesthesia in Improving Surgical Outcome

PANELS

ANESTHESIA MACHINES AND VENTILATORS — Saturday AM, March 9
NW Lawson, MD, Moderator; JJ Andrews, MD, J Condurso, North American Drager, and JB Biondi, Ohmeda

YOU, THE ANESTHESIOLOGIST IN COURT — A MOCK MEDICAL MALPRACTICE TRIAL
(Based on an actual case) — Saturday PM, March 9
DH Morrow, MD, Moderator; Hon. D Hittner, F Stein, MD, TP Sartwelle, Esq., RJ Swift, Esq.

EMERGENCY AIRWAY MANAGEMENT — Monday AM, March 11
MS Gorback, MD, Moderator; JL Benumof, MD, EJ Krane, MD, CB Watson, MD

LEGISLATIVE UPDATE — LUNCHEON SESSION — Sunday, March 10
BP Stephenson, MD, and AC Lang, representing American Society of Anesthesiologists

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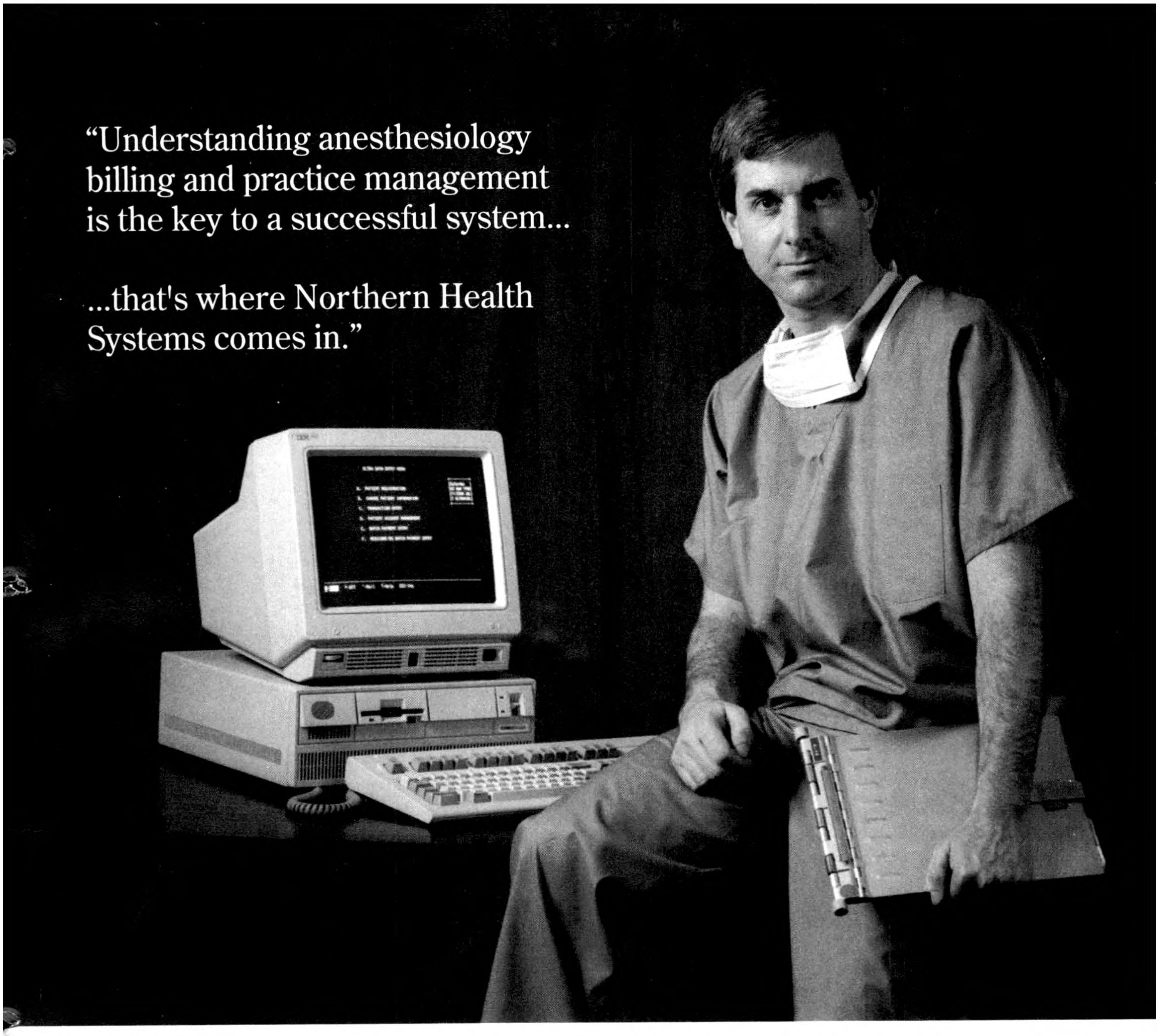
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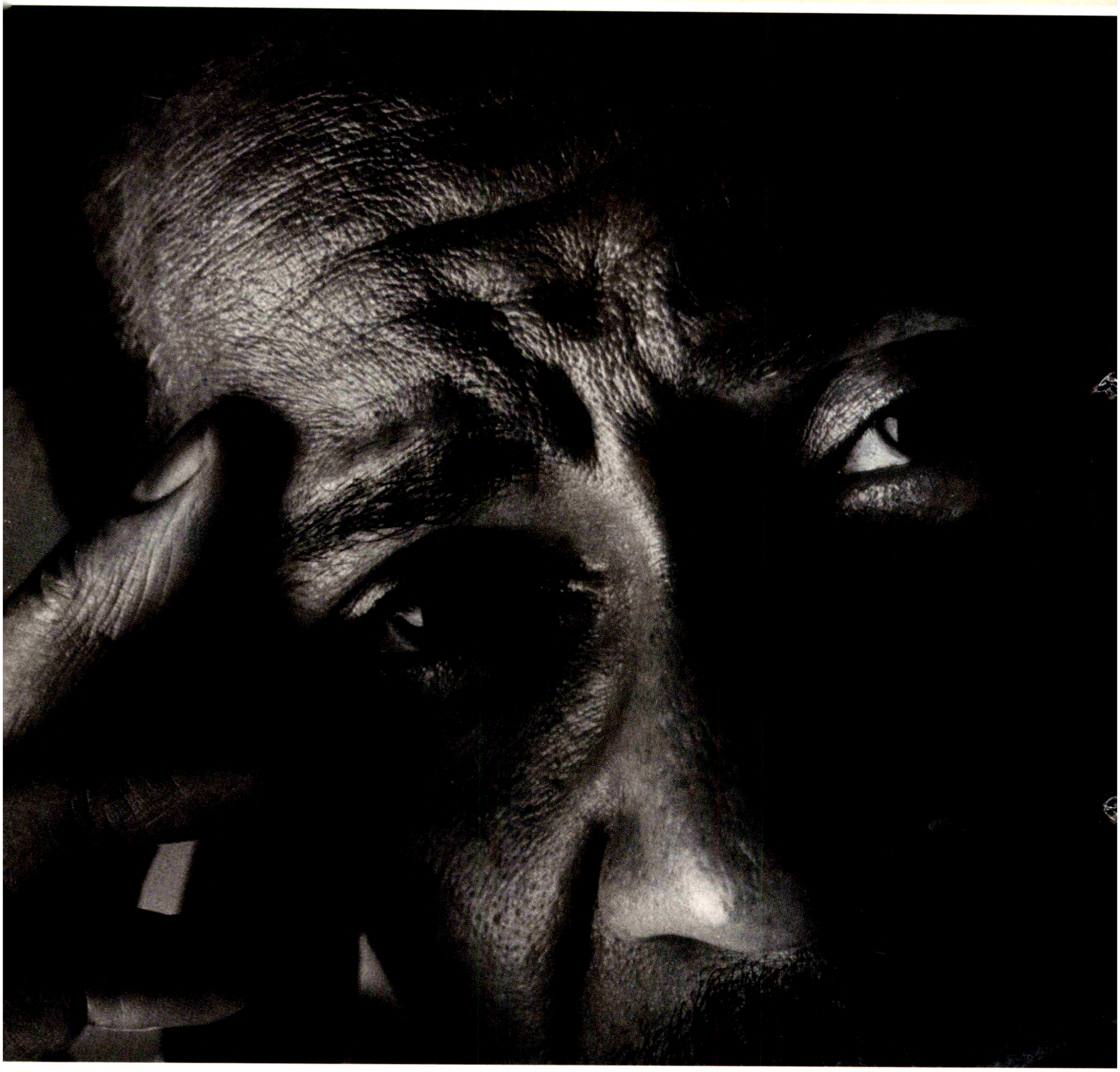

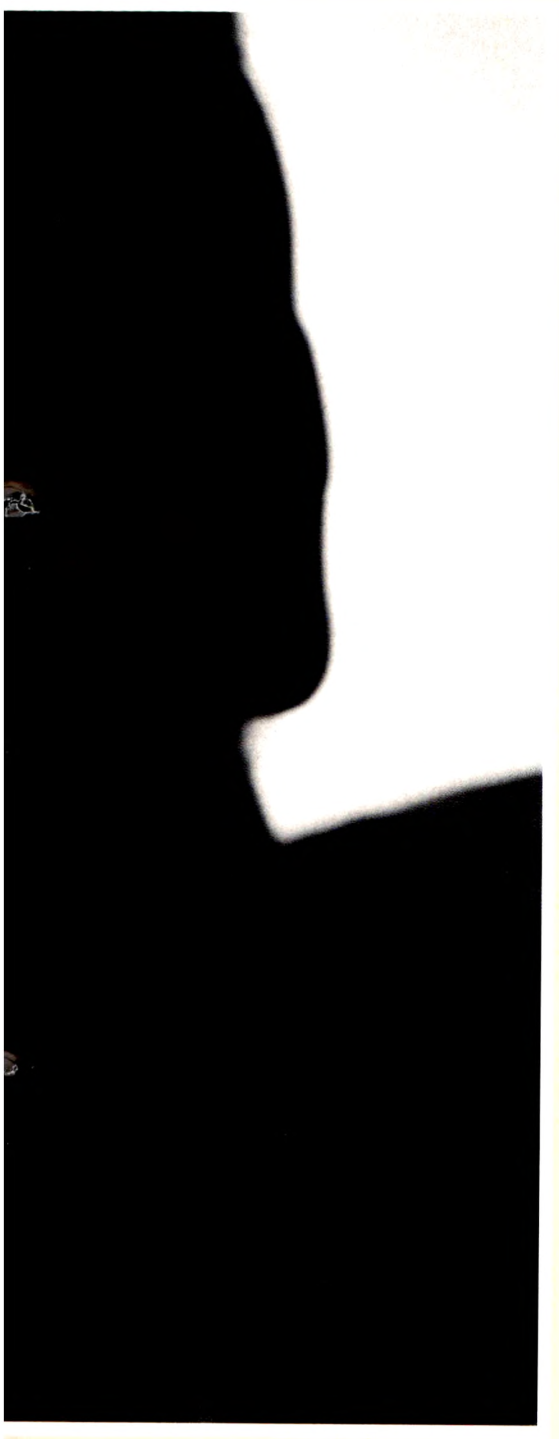

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CONTRAINDICATIONS

HESPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. HESPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS

Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing) bleeding due to hemodilution (see Warnings), and circulatory overload and pulmonary edema (see Precautions).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis

250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The safety and compatibility of other additives have not been established.

HOW SUPPLIED

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

HESPAN is supplied sterile and nonpyrogenic in 500 mL intravenous plastic infusion containers (NDC 0056-0037-44) and 500 mL intravenous glass bottles (NDC 0056-0037-05).

CAUTION

Federal (USA) law prohibits dispensing without prescription.

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ANESTH ANALG 451
1990;71:451–9

Isoflurane-Induced Vasodilation: Role of the α-Adrenergic Nervous System

Debra A. Schwinn, MD, R. William McIntyre, MD, and J. G. Reves, MD

SCHWINN DA, McINTYRE RW, REVES JG. Isoflurane-induced vasodilation: role of the α-adrenergic nervous system. Anesth Analg 1990;71:451–9.

Isoflurane is a potent systemic vasodilator. Because isoflurane vasodilation is clinically significant, we sought to explore whether decreases in systemic vascular resistance caused by isoflurane involve the α-adrenergic nervous system in humans. Specifically, we tested the hypothesis that isoflurane systemic vasodilation is mediated via inhibition of vascular α_1-adrenergic responsiveness. Phenylephrine pressor dose-response curves were established before anesthesia and during isoflurane/oxygen anesthesia in patients undergoing coronary artery bypass surgery; all patients included in the study ($n = 11$) demonstrated significant ($P = 0.0001$) decreases in systemic vascular resistance when isoflurane was given in concentrations adequate to produce a 20% decrease in mean arterial blood pressure. Polynomial regression of the phenylephrine dose-response curve was used to estimate the phenylephrine dose required to increase mean arterial blood pressure 15 mm Hg, designated $PD_{15\,\mathrm{mm\,Hg}}$. Each patient served as his or her own control. Preanesthetic baseline $PD_{15\,\mathrm{mm\,Hg}}$ values (115 ± 23 μg [1.4 ± 0.3 μg/kg], mean ± SEM) were not significantly different from isoflurane $PD_{15\,\mathrm{mm\,Hg}}$ values (124 ± 20 μg [1.5 ± 0.3 μg/kg]). End-tidal isoflurane concentration ranged from 0.6%–1.5%; isoflurane $PD_{15\,\mathrm{mm\,Hg}}$ was not correlated with end-tidal isoflurane concentration. Patient characteristics and hemodynamics did not affect $PD_{15\,\mathrm{mm\,Hg}}$. These results suggest that isoflurane-induced systemic vasodilation is not mediated via inhibition of α_1-adrenergic responsiveness, disproving our hypothesis. This finding has clinical importance because it demonstrates that α_1-adrenergic stimulation with phenylephrine is effective in correcting hypotension in patients receiving isoflurane anesthesia.

Key Words: ANESTHETICS, VOLATILE—isoflurane. RECEPTORS, α_1-ADRENERGIC. SYMPATHETIC NERVOUS SYSTEM, VASOCONSTRICTORS—phenylephrine. ARTERIES, VASODILATION—isoflurane.

The volatile anesthetic agent isoflurane is a potent systemic vasodilator (1–5), yet the mechanisms for this effect remain to be elucidated. Isoflurane maintains or decreases vascular resistance in renal (5–7), cardiac (6,8), cerebral (8,9), skin (10), muscle (11), and possibly mesenteric (6,7) vasculature. Whereas spontaneous arteriolar (vessels less than 25 μm in diameter) vasomotion is abolished by halothane, it is not affected by isoflurane (12). This suggests that isoflurane possibly decreases systemic vascular resistance (SVR) in larger arteries.

The adrenergic nervous system is intimately involved in the control of vascular tone and may be responsible for isoflurane-mediated decreases in SVR. In particular, α_1-adrenergic receptors have been shown to play an important role in vascular tone and the regulation of blood pressure (13,14). Although isoflurane has been shown to have no β-adrenergic blocking activity in the dog (15) and no direct action on α- or β-adrenoceptors in the isolated rat parotid gland (16), α-adrenergic effects of isoflurane have been shown in other models. Isoflurane stimulates α-adrenergic mediated increases in vascular resistance in isolated rat and dog mesenteric artery preparations (17,18). Isoflurane also has been demonstrated to attenuate phenylephrine-evoked contraction in isolated dog epicardial coronary arteries, a

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Supported by Stuart Pharmaceuticals and by fellowship grants to D.A.S. from the Society of Cardiovascular Anesthesiologists and from the American Society of Anesthesiologists/Association of University Anesthetists.

Presented in part at the Annual Meeting of the Society of Cardiovascular Anesthesia, New Orleans, Louisiana, 1988; and the American Society of Anesthesiologists Annual Meeting, San Francisco, California, 1988.

Received from the Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Heart Center of the Duke University Hospital, Durham, North Carolina. Accepted for publication July 2, 1990.

Address correspondence to Dr. Schwinn, Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Box 3094, Heart Center of the Duke University Hospital, Durham, NC 27710.

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response found to be mostly vascular endothelium-dependent (19).

Because isoflurane vasodilation is clinically significant, we sought to explore whether decreases in SVR by isoflurane involve the α-adrenergic nervous system in humans. Specifically, we tested the hypothesis that isoflurane systemic vasodilation is mediated via inhibition of vascular α_1-adrenergic responsiveness.

Materials and Methods

Study Population

After institutional approval and informed patient consent, 11 patients undergoing coronary artery bypass graft surgery were enrolled in the study. Patients with unstable angina, receiving intraaortic balloon counterpulsation, requiring intravenous nitroglycerin or inotropic agents, or receiving α-adrenergic blocking medications were excluded from the study. All patients had good ventricular function as evidenced by a preoperative ejection fraction ≥40%.

Protocol

Patients received intramuscular morphine (0.1 mg/kg), intramuscular scopolamine (0.2–0.4 mg), and oral diazepam (0.15 mg/kg) within 2 h of induction of anesthesia. All patients breathed oxygen at 3 L/min via nasal cannulae starting at the time of anesthetic premedication, which was continued until induction of anesthesia. With the patient on the operating room table in a preinduction room immediately adjacent to each operating room, intravenous (IV) radial arterial and pulmonary arterial catheters were inserted, and a five-lead electrocardiogram (ECG) was applied. Approximately 1.0 mL of 1% lidocaine HCl was used subcutaneously during catheter insertions in all patients. Continuous ECG monitoring with ST segment analysis of leads I, II, and V was accomplished using a Marquette monitor. Cardiac outputs were measured using the thermodilution method. (-) Phenylephrine HCl (Winthrop Laboratories, New York, N.Y.) was diluted to 10 μg/mL in normal saline.

With patients in the supine position, resting quietly with dimmed lighting, baseline heart rate, mean arterial blood pressure (MAP), central venous pressure, pulmonary artery diastolic pressure, pulmonary artery occlusion pressure, cardiac output (CO), and plasma catecholamine levels were measured. A phenylephrine dose-response curve was then generated (denoted "baseline phenylephrine pressor dose-response curve" [baseline PDRC]) using a phenylephrine bolus technique previously described (20). In brief, 20 μg of phenylephrine was injected intravenously via the side-port of an internal jugular vein introducer cannula (Arrow), and the peak MAP occurring in the ensuing 2 min was recorded. Five minutes later, after MAP had returned to baseline value, a second bolus dose of phenylephrine (40 μg) was given. Again the peak MAP achieved in the ensuing 2 min was recorded. Five minutes later, once hemodynamic parameters had returned to baseline, a third phenylephrine dose (80 μg) was given. This was continued through the phenylephrine dose range: 20, 40, 80, 120, 160, 200, 240, 280, 320, or 360 μg, or until peak MAP response to phenylephrine increased 20% above baseline. At this point the phenylephrine dose-response curve was considered complete.

Patients were then moved from the preinduction room into the operating room, and preoxygenation was begun with mask oxygen at 6 L/min. New preisoflurane baseline hemodynamics (heart rate, MAP, central venous pressure, pulmonary artery diastolic pressure, and CO) were measured at this time, denoted "preisoflurane baseline." Anesthesia was then induced with oxygen, nitrous oxide, and gradually increasing concentrations of isoflurane via mask with spontaneous ventilation. After loss of response to verbal command, nitrous oxide was discontinued, oxygen and isoflurane were continued, vecuronium was administered intravenously, and the patient's trachea was intubated. End-tidal isoflurane concentration was measured using an Engstrom EMMA (accuracy 0.1 vol %; Engstrom Medical AB, Bromma, Sweden). The concentration of isoflurane was adjusted to produce a 20% decrease in MAP. Ten minutes after intubation, and before surgical incision, postisoflurane hemodynamics were recorded, blood for measurement of plasma catecholamine levels was drawn, and a second phenylephrine dose-response curve (denoted "isoflurane phenylephrine pressor dose-response curve" [isoflurane PDRC]) was generated as previously described. Subsequently, anesthesia was maintained with intravenous fentanyl and isoflurane as required. Postoperatively, patients were taken to the intensive care unit and tracheal extubation occurred approximately 6–16 h later. Postoperative ECGs were examined for evidence of myocardial infarction.

Patient Characteristics

Specific definitions of medical conditions were used in this study. Hypertension was defined as blood pressure greater than 140/90 mm Hg documented on at least three occasions or a history of increased blood pressure requiring medication. Diabetes mellitus was considered present if a patient required oral hypoglycemic or insulin medication. Myocardial infarction was considered to have occurred if there was ECG evidence of an old myocardial infarction or previously documented episodes of increased CPK-MB isoenzymes without concurrent ECG changes. Congestive heart failure was defined as the presence of at least three of the following: chest x-ray evidence of either pulmonary edema or four-chamber myocardial enlargement; evidence on physical examination of audible rales, pedal edema, congestive hepatomegaly, S_3 gallop, jugular venous distention, or hepatojugular reflux; increased central venous pressure; increased left ventricular end-diastolic pressure or pulmonary artery occlusion pressure unaccompanied by evidence of myocardial ischemia—left ventricular end-diastolic pressure > 18 mm Hg during cardiac catheterization, or pulmonary artery occlusion pressure > 18 mm Hg upon insertion of the pulmonary artery catheter on the day of surgery.

Plasma Catecholamine Determinations

Blood samples for plasma catecholamine determinations were collected in 5 mL of chilled polypropylene tubes containing anticoagulant (EGTA) and antioxidant (glutathione). After refrigerated centrifugation, the plasma was transferred to plastic storage tubes and stored at −70°C until the time of assay. Thawed plasma samples for measurement of catecholamine levels were mixed with 10 mL of phosphate buffer (0.1 M, pH 7) and separated on a Bio-Rex 70 ion-exchange column. The column was washed with water, and then 1 mL of sulfuric acid (0.7 M) was added. The catecholamines were eluted with ammonium sulfate (1 M) into tubes containing ethylenediaminetetraacetic acid/sodium metabisulfite, alumina, and TRIS buffer (3 M, pH 8.5). After microfiltration, 200 μL of perchloric acid (0.1 M) was added to the solution. The perchlorate-catecholamine solution was injected onto a high-performance liquid chromatography column (stationary phase—C_{18} column, mobile phase—monochloroacetic acid [0.15 M, pH 3] with sodium octyl sulfate) for determination of norepinephrine and epinephrine levels. Plasma catecholamine assay sensitivity was 30 pg/mL, and the coefficient of variation was 9%.

Data Analysis

The amount of phenylephrine required to increase MAP by 15 mm Hg (denoted pressor dose 15 mm Hg, $PD_{15\ mm\ Hg}$) was calculated using second-order polynomial regression of the phenylephrine log dose-response curve. Polynomial regression with or without logarithmic transformation has been shown to be superior to linear regression in analyzing pressor dose-response curves (21). Paired *t*-tests were used to compare baseline, preisoflurane, and postisoflurane hemodynamic variables and $PD_{15\ mm\ Hg}$ in each patient. Linear regression analysis was used to test for relationships between end-tidal isoflurane concentration and isoflurane $PD_{15\ mm\ Hg}$, and between continuous patient characteristic variables and $PD_{15\ mm\ Hg}$. The nonparametric form of analysis of variance (Kruskal–Wallis test) was used to test for relationships between category patient-characteristic variables (gender, medical condition, and medication) and $PD_{15\ mm\ Hg}$. Statistical significance was declared with $P < 0.05$.

Results

Patient Outcome

All patients were well sedated upon arrival in the preinduction room, but were easily aroused and fully responsive to command. No patient complained of chest pain, had ST segment depression or elevation, or had an increase in baseline premature ventricular contractions during the phenylephrine dose-response studies. There was no ECG evidence of perioperative myocardial infarction, and no operative mortality. There were no perioperative or postoperative complications attributable to the administration of phenylephrine. Eleven patients completed the study.

Patient Characteristics and Hemodynamics

Table 1 summarizes patient characteristics including general characteristics, medical history, preoperative medication, laboratory values, and surgical characteristics. Pertinent hemodynamic measurements and catecholamine levels for various phases of the study are listed in detail in Table 2. Important hemodynamic changes occurred during this study (Table 2). During generation of the baseline PDRC, MAP was 83.9 ± 3.1 mm Hg (mean ± SEM). Each patient, supine on the operating table in the preinduction room, rested quietly during this aspect of the study. To generate the isoflurane PDRC, patients were moved into the operating room and preoxygenated via mask. Significant ($P = 0.0003$) increases in MAP (94.5 ± 3.5 mm Hg, mean ± SEM) above baseline levels but without significant heart rate changes occurred during preoxygenation (preisoflurane) in spite

Table 1. Preoperative Patient Characteristics (n = 11)

General	
Sex—male	10
Age (yr)	59.3 ± 7.9
Weight (kg)	80.7 ± 14.8
Medical history	
Ejection fraction (%)	54.9 ± 8.3
Hypertension	6
Diabetes	2
Myocardial infarction	7
Congestive heart failure	0
Preoperative medication	
Calcium channel blockers	9
β-Adrenergic blockers	9
Diuretics	0
Nitrates	6
Digoxin	1
Laboratory values	
Hematocrit (%)	40.8 ± 4.5
Potassium (mEq/L)	3.8 ± 0.4
Surgery	
No. vessels bypassed	3.0 ± 1.1

Values are given as number of patients or as mean ± SD.

of clinical evidence of adequate sedation. Induction with isoflurane via spontaneous mask ventilation was accomplished in 11 patients and resulted in an approximately 20% decrease in MAP (73.4 ± 2.6 mm Hg, mean ± SEM, $P = 0.0003$) by study design, below preisoflurane values. Cardiac output did not change significantly at any point in this study, confirming that decreases in MAP with isoflurane administration were the result of decreased SVR in these patients. Pulmonary artery diastolic pressure increased significantly (Table 2) between baseline and preisoflurane measurements, but no further changes in pulmonary artery diastolic pressure occurred with isoflurane anesthesia in either group.

Phenylephrine Pressor Dose 15 mm Hg Values

Results of individual and composite phenylephrine pressor dose-response curves during baseline and during isoflurane anesthesia for all 11 patients are shown in Figure 1. Pressor dose 15 mm Hg was calculated using second-order polynomial regression analysis of the log phenylephrine pressor dose-response curves. Baseline $PD_{15\ \mathrm{mm\ Hg}}$ was 115 ± 23 μg (1.4 ± 0.3 μg/kg, mean ± SEM), and isoflurane $PD_{15\ \mathrm{mm\ Hg}}$ was 124 + 20 μg (1.5 ± 0.3 μg/kg) (Table 2), indicating that there was no significant effect on $PD_{15\ \mathrm{mm\ Hg}}$ by isoflurane. This is further emphasized by virtually overlapping composite regression curves for PDRCs generated during baseline and isoflurane time periods. Hence, the same amount of phenylephrine was required to increase MAP 15 mm Hg at baseline and during isoflurane in these patients.

Catecholamines

Norepinephrine and epinephrine plasma levels were measured just before generation of the baseline

Table 2. Hemodynamic Variables and Plasma Catecholamine Levels (n = 11)

				P value		
	Baseline (B)	Preisoflurane (P)	Isoflurane (I)	B:P	B:I	P:I
MAP (mm Hg)	83.9 ± 3.1	94.5 ± 3.5	73.4 ± 2.6	0.025	0.047	0.0003
SVR (dyne·s·cm^{-5})	1405 ± 83	1637 ± 122	1297 ± 120	NS	NS	0.0001
Pulse (beats/min)	56.6 ± 3.8	58.7 ± 4.3	60.4 ± 4.8	NS	NS	NS
PADP (mm Hg)	9.4 ± 1.0	14.4 ± 1.4	14.9 ± 0.7	0.0004	0.001	NS
PAOP (mm Hg)	11.9 ± 1.0	[a]	15.0 ± 1.0		NS	
CVP (mm Hg)	8.3 ± 1.0	9.0 ± 1.1	10.5 ± 0.8	NS	NS	NS
CO (L/min)	4.3 ± 0.3	4.3 ± 0.2	4.0 ± 0.3	NS	NS	NS
$PD_{15\ \mathrm{mm\ Hg}}$						
μg	115 ± 23		124 ± 20		NS	
μg/kg	1.39 ± 0.25		1.54 ± 0.27		NS	
NE (pg/mL plasma)	414 ± 71		471 ± 106		NS	
E (pg/mL plasma)	115 ± 26		77 ± 20		NS	
End-tidal isoflurane concentration (%)			1.8 ± 0.2			

Values for baseline, preisoflurane$_2$, and isoflurane are given as mean ± SEM, and evaluated with paired t-test.

By study design, MAP decreased 20% in all patients during isoflurane anesthesia compared to preisoflurane MAP. Baseline (B) measurements were taken with patients resting quietly on the operating room table in a quiet preinduction area with dimmed lighting. Preisoflurane (P) measurements were taken in the operating room during preoxygenation via mask, immediately before isoflurane induction. Isoflurane (I) measurements were taken 10 min postintubation, once MAP decreased 20% compared with preisoflurane values.

MAP, mean arterial blood pressure; SVR, systemic vascular resistance; PADP, pulmonary artery diastolic pressure; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; CO, cardiac output; NE, norepinephrine; E, epinephrine; $PD_{15\ \mathrm{mm\ Hg}}$, pressor dose 15 mm Hg; NS, not significant at the 95% confidence level.

[a] Pulmonary artery occlusion pressure was not measured in every patient at this time point.

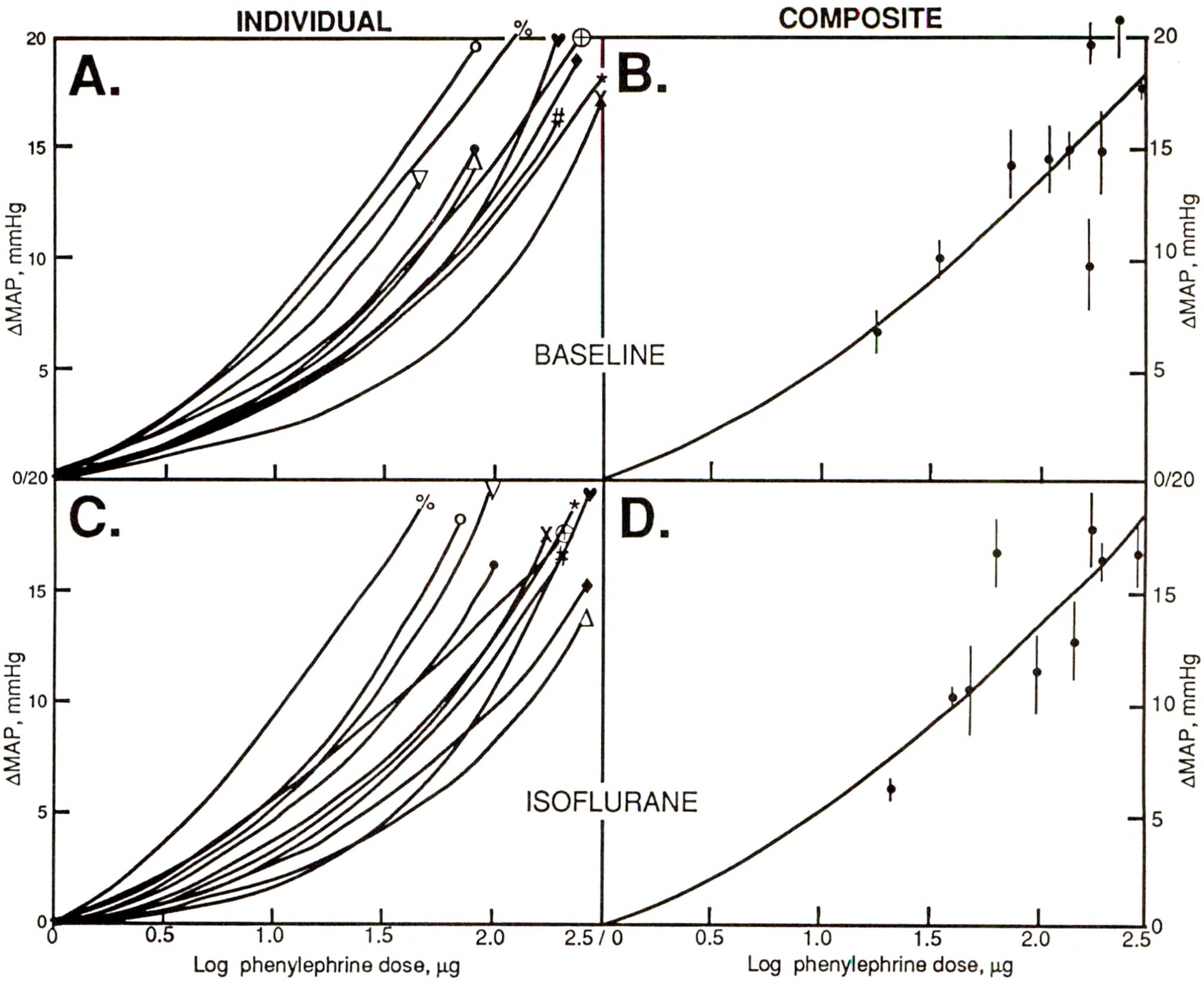

Figure 1. Individual and composite phenylephrine PDRC before and during isoflurane anesthesia for all 11 patients enrolled in the study. Log phenylephrine dose (µg) is plotted on the x-axis and Δ MAP on the y-axis. For clarity of presentation in individual PDRCs (**A** and **C**), only the second-order polynomial regression lines are shown. Symbols (●, X, ○, #, %, △, ▽, *, ♦, ♥, ⊕) denote individual patient dose-response curves; the placement of symbols corresponds to the end of that patient's PDRC (associated with a 20% increase in MAP as defined in the text). Data points in composite curves (**B** and **D**) represent mean values ± SEM for all patients for each phenylephrine dose. No effect of isoflurane on individual PDRCs (paired *t*-tests, Table 2) or composite PDRC regression lines (**B** and **D**) was noted. Phenylephrine pressor dose 15 mm Hg ($PD_{15\ mm\ Hg}$) was calculated individually for each patient and resulting values are presented in Table 2 as mean ± SEM.

PDRC and isoflurane PDRC. No significant differences in either norepinephrine or epinephrine levels were seen between these time periods (Table 2).

Effect of End-Tidal Isoflurane Concentration, Patient Characteristics, and Hemodynamics on Phenylephrine Pressor Dose 15 mm Hg

End-tidal isoflurane concentrations ranged from 0.8% to 2.3%. Mean arterial blood pressure decreased significantly during isoflurane anesthesia by study design; however, neither SVR nor isoflurane $PD_{15\ mm\ Hg}$ was correlated with end-tidal isoflurane concentration in either group. There were no effects of patient characteristics or hemodynamic variables on either preisoflurane $PD_{15\ mm\ Hg}$ or isoflurane $PD_{15\ mm\ Hg}$.

Discussion

These results suggest that isoflurane systemic vasodilation is not mediated via inhibition of α_1-adrenergic responsiveness, hence disproving our hypothesis. Pre-

P_2 24,554

vious work (16) has shown that isoflurane has no direct action on α- or β-adrenoceptors in isolated rat parotid gland; our results suggest this may be true in human systemic vasculature. This stands in contrast to isoflurane attenuation of the mostly endothelium-dependent phenylephrine-evoked contraction in isolated dog epicardial coronary arteries (19).

Phenylephrine Pressor Dose Response

Bolus phenylephrine administration was used to assess α_1-adrenergic responsiveness in this study. Phenylephrine, an α_1-adrenergic agonist (22,23), has been administered as a continuous infusion to assess adrenergic responsiveness in both clinical and laboratory settings. Because continuous infusion of pressors to patients with myocardial disease may increase afterload and potentially increase myocardial wall stress and myocardial oxygen consumption, a shorter duration of peak mean blood pressure effect of phenylephrine as achieved with bolus injections is desirable in these patients. Continued infusion of phenylephrine may also lead to tolerance (24) or desensitization of α_1-adrenergic receptors, a process that can be minimized using a bolus technique. For these reasons, a previously validated (20,25) bolus technique of phenylephrine administration was used to assess α_1-adrenergic responsiveness in this study. Figure 1 illustrates individual and composite phenylephrine bolus PDRCs during baseline and isoflurane administration in 11 patients. Because our end point of a 20% increase in MAP was artificially imposed as maximum MAP by study design (for patient safety reasons), it does not represent a true 100% effect. A complete dose-response curve for phenylephrine and other α_1-adrenergic agents has been done in rats. These experiments reveal that baseline diastolic blood pressure (DBP) in intact pithed rats is 40 mm Hg, and that maximum increases with α_1-adrenergic agonists range between Δ + 100–140 mm Hg for a maximum DBP of 180 mm Hg (26–30). In dogs, continuous infusions of angiotensin II result in elevations of MAP from a baseline of 90 on day 1 to 160 on day 4; further elevations were limited by pulmonary edema (31). In humans, finding the maximum blood pressure response to α_1-adrenergic agonists is limited by ethical considerations. However, reports of patients with uncontrolled malignant hypertension (DBP $>$ 130 mm Hg) (32) suggest that, in rare cases, maximum systolic blood pressure may be approximately 250–300 mm Hg. The $PD_{15\ mm\ Hg}$ value calculated in this study is the highest possible ΔMAP that could be calculated in *every* patient (for example a 20% increase in MAP in patients with a starting MAP of 75 is 15 mm Hg). It also represents the closest value to ED_{50} obtainable in this study.

Blood Pressure—CO and Systemic Vascular Resistance Components

It is important to note that α_1-adrenergic responsiveness is a clinical marker of end organ responses. Mean arterial blood pressure has two major components—CO and SVR. Two important aspects of this study relate to this concept. First, MAP was used as an end point for generation of phenylephrine PDRCs instead of SVR. Systemic vascular resistance and MAP peak simultaneously after bolus phenylephrine administration in cardiac surgery patients when near continuous CO measurement with esophageal Doppler is employed (25). Although minor increases in CO may occur with direct stimulation of inotropy via myocardial α_1-adrenergic receptors (33–37), this is not thought to be clinically significant especially in the phenylephrine dose range used in this study. Because it is impossible to predict when peak MAP will occur after phenylephrine bolus administration, an accurately timed thermodilution CO is difficult, and therefore the resulting SVR calculation may not represent the actual peak SVR. Hence, in the setting of bolus phenylephrine administration, MAP provides a more accurate hemodynamic marker for vascular responsiveness than SVR.

A second important aspect of this study related to the two major determinants of MAP (CO and SVR) pertains to patient selection. All 11 patients in our study were anesthetized with isoflurane and responded with a 20% decrease in MAP, and isoflurane-induced decreases in SVR. Only in patients with isoflurane-induced decreases in SVR could our hypothesis be tested regarding involvement of the α_1-adrenergic nervous system in isoflurane-induced vasodilation. Hence, patients who might respond to isoflurane with decreases in CO instead of SVR would not have been good candidates in which to test our hypothesis. Hence, careful patient selection is important in studies pertaining to vascular responsiveness in order to ensure that proper conclusions can be drawn.

There is one drawback to using MAP in our study as a measure of α_1-adrenergic responsiveness. Diastolic blood pressure may be a more sensitive marker of α_1-mediated vasoconstriction than MAP. It is therefore possible that small, subtle changes in α_1-adrenergic responsiveness might have been missed by using MAP as the vascular end point rather than

DBP. This drawback is balanced by two major considerations in designing our study. First, because isoflurane is known to decrease SVR and MAP is used in the calculation of SVR, using MAP instead of DBP provided an accurate means to calculate SVR. Second, MAP is a more commonly used clinical marker of blood pressure in humans than DBP. Hence, we chose MAP as our marker of vascular responsiveness to α_1-adrenergic agents.

End-Tidal Isoflurane Concentration

End-tidal isoflurane concentration was adjusted to produce a 20% decrease in MAP as described above. A hemodynamic end point was chosen in this study rather than an arbitrary mean alveolar concentration value because mean alveolar concentration reflects brain anesthetic concentration and our study focuses on the peripheral vascular effects of isoflurane. A vascular marker of isoflurane concentration may also eliminate possible confounding isoflurane pharmacokinetic differences between patients. In addition, because each patient served as his or her own control, any differences between patients in the absolute amount of isoflurane present would not influence the validity of the results. It is of interest that end-tidal isoflurane was not correlated with isoflurane $PD_{15\ mm\ Hg}$.

Patient Characteristics, Hemodynamic Variables, and Pressor Dose 15 mm Hg

Several interesting hemodynamic changes occurred during the study. Specifically, MAP increased significantly between baseline and preisoflurane time points (Table 2). The operating room table upon which the patient rested supine was moved into the operating room, and oxygen was applied via face mask between baseline and preisoflurane time points. Although each patient appeared to be adequately sedated, MAP increased with these manipulations. Although not significant, a trend of increased SVR occurred at the preisoflurane time point compared with baseline; CO did not change. One explanation for these results would be a sudden increase in catecholamine levels during this time point. However, norepinephrine and epinephrine plasma levels were measured only just before generation of PDRCs and not during the preisoflurane time point. Therefore, the exact etiology of the hemodynamic changes at the preisoflurane time point cannot be elucidated. Preisoflurane MAP was used as a new baseline from which to judge the hemodynamic effects of isoflurane; in other words a 20% decrease in MAP during the isoflurane time point (10 min after intubation, just before generation of the isoflurane PDRC) was measured from preisoflurane values. This was an important control in our study in order to monitor the acute effects of isoflurane in each patient.

There was no effect of patient characteristics or hemodynamic variables on either baseline $PD_{15\ mm\ Hg}$ or isoflurane $PD_{15\ mm\ Hg}$. These results are somewhat surprising. Hypertension (38,39) and aging (40,41) have been associated with increased circulating catecholamines and possible alterations in vascular responsiveness. In addition, it has been shown that isoflurane influences central and regional hemodynamics differently in hypertensive as compared with normotensive rats (42). Although neither hypertension nor age affected $PD_{15\ mm\ Hg}$ in our study, a larger patient group is needed to study these effects more fully.

Phenylephrine Pressor Dose 15 mm Hg

An important physiologic issue remains in analyzing the results of this study. This is illustrated by the following question. Does an absolute 15 mm Hg increase in MAP represent the same degree of vessel contraction at two different starting MAPs? In this study, baseline MAP during isoflurane anesthesia was lower than baseline preisoflurane MAP in every patient by study design. Therefore, is $PD_{15\ mm\ Hg}$ comparable between these two time periods independent of the presence of isoflurane? This question was first addressed in the 1950s by Wilder (43), who showed that the higher the prestimulus level of a variable such as MAP, the smaller the tendency to increase further on function-raising stimuli. This principle, the law of initial value, can also be viewed in terms of refractoriness. The greater the stimulus (i.e., the higher the baseline MAP), the more refractory the tissue to further stimulus (i.e., the smaller the response to a vasoconstrictor). This concept may present a potential weakness in our study, one that is quite difficult to overcome in testing our hypothesis in patients. However, evaluation of the entire PDRC using ΔMAP (as shown in Figure 1) suggests this is not the case in this patient population.

Possible Mechanisms of Isoflurane Vasodilation

As isoflurane-induced vasodilation does not appear to be mediated via inhibition of α_1-adrenergic responsiveness, how is this effect achieved? There are several possible mechanisms by which isoflurane might induce vasodilation. The first possible mechanism is by direct arteriolar relaxation. Decreases in SVR seen with isoflurane could be explained by this hypothesis. However, isoflurane may interact with or inhibit other systems responsible for vasoconstriction such as α_2-adrenergic agonists, angiotensin II, endothelin, or renin. It could also interact with vasodilators such as atrial natriuretic factor or endothelial relaxing factor or calcium channels, although one study suggests that isoflurane vasodilation is mediated by mechanisms other than calcium-entry blockade (44). Elucidation of these mechanisms clearly requires further study.

In conclusion, these results suggest that isoflurane systemic vasodilation is not mediated via inhibition of α_1-adrenergic responsiveness, hence disproving our hypothesis. This finding is clinically important because it demonstrates that α_1-adrenergic stimulation with phenylephrine will be effective in correcting hypotension in patients receiving isoflurane anesthesia and that the expected response will be similar to that in the unanesthetized state.

The authors gratefully acknowledge the technical assistance provided by Eric D. Hawkins and the secretarial assistance of Susan Roberts and Bonnie Turner. They also wish to acknowledge their anesthesiology associates Drs. Clements, DeBruijn, Hill, Karis, and surgical colleagues Drs. Jones, Lowe, Oldham, Rankin, Van Tright, and Wechsler for their cooperation during the study.

References

1. Eger EI II. Isoflurane: a review. Anesthesiology 1981;55:559–76.
2. Eger EI II. The pharmacology of isoflurane. Br J Anaesth 1984;56:71S–99S.
3. Reiz S, Ostman M. Regional coronary hemodynamics during isoflurane-nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 1985;64:570–6.
4. Markschies HA, Hess W, Schulte SU, Tarnow J. Blood pressure control with an inhalational anesthetic in acute intraoperative hypertension. Hemodynamic profile of halothane, enflurane and isoflurane in coronary artery surgery patients. Anaesthetist 1984;33:284–90.
5. Priebe HJ. Differential effects of isoflurane on regional right and left ventricular performances, and on coronary, systemic, and pulmonary hemodynamics in the dog. Anesthesiology 1987;66:262–72.
6. Theye RA, Michenfelder JD. Individual organ contributions to the decrease in whole-body V_{O_2} with isoflurane. Anesthesiology 1974;40:571–4.
7. Ostman M, Biber B, Martner J, Reiz S. Influence of isoflurane on renal and intestinal vascular responses to stress. Br J Anaesth 1986;58:630–8.
8. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984;63:557–65.
9. Cucchiara RF, Theye RA, Michenfelder JD. The effects of isoflurane on canine cerebral metabolism and blood flow. Anesthesiology 1974;40:571–4.
10. Stevens WC, Cromwell TH, Halsey MJ, et al. The cardiovascular effects of a new inhalational anesthetic, forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 1971;35:8–16.
11. Tarnow J, Bruckner JB, Eberlein HJ, et al. Haemodynamics and myocardial oxygen consumption during isoflurane anaesthesia in geriatric patients. Br J Anaesth 1976;48:669–75.
12. Bohrer H, Frost L, Funk W. Direct observation of microcirculation in isoflurane anaesthesia. Anaesth Intensivther Notfallmed 1987;22:84–9.
13. Tsujimoto G, Bristow MR, Hoffman BB. Identification of alpha-1 adrenergic receptors in rabbit aorta with [125I] BE 2254. Life Sci 1984;34:639–46.
14. Reid JL. Alpha-adrenergic receptors and blood pressure control. Am J Cardiol 1986;57:6E–12E.
15. Philbin DM, Lowenstein E. Lack of beta-adrenergic activity of isoflurane in the dog: a comparison of circulatory effects of halothane and isoflurane after propranolol administration. Br J Anaesth 1976;48:1165–70.
16. Ostman M, Henriksson R, Sundstrom S, Reiz S. Isoflurane—a study of its adrenoceptor interaction in the isolated rat parotid gland. Anesthesiology 1986;64:734–8.
17. Tverskoy M, Gelman S, Fowler KC, Bradley EL. Intestinal circulation during inhalational anesthesia. Anesthesiology 1985;62:462–9.
18. Biber B, Schaefer CF, Smolik MJ, et al. Dose-related effects of isoflurane on superior mesenteric vasoconstriction induced by endotoxemia in the rat. Acta Anaesthsiol Scand 1987;31:430–7.
19. Blaise G, Sill JC, Nugtent M, Van Dyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
20. Schwinn DA, McIntyre RW, Hawkins ED, Kates RA, Reves JG. α_1-Adrenergic responsiveness during coronary artery bypass surgery: effect of preoperative ejection fraction. Anesthesiology 1988;69:206–17.
21. Sumner DJ, Elliot HL, Reid JL. Analysis of the pressor dose response. Clin Pharmacol Ther 1982;32:450–8.
22. Starke K, Docherty JR. Alpha$_1$- and alpha$_2$-adrenoceptors: pharmacology and clinical implications. J Cardiovasc Pharmacol 1981;3(Suppl 1):514–23.
23. Ekenvall L, Lindblad LE. Is vibration white finger a primary sympathetic nerve injury? Br J Ind Med 1986;43:702–6.
24. Baker R, Mendel B. Some observations on 'autoregulatory escape' in cat intestine. J Physiol (London) 1967;190:229–40.
25. Schwinn DA, Reves JG. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg 1989;68:571–8.
26. Pedrinelli R, Tarazi RC. Interference of calcium entry blockade in vivo with the pressor responses to α-adrenergic stimulation: effects of two unrelated blockers on responses to both exogenous and endogenously released norephinephrine. Circulation 1984;69:1171–6.
27. Vanhoutte PM. Calcium-entry blockers, vascular smooth muscle and systemic hypertension. Am J Cardiol 1985;55:17B–23B.
28. Cavero I, Shepperson N, Lefevre-Borg F, Langer SZ. Differential inhibition of vascular smooth muscle responses to α_1- and α_2-adrenoceptor agonists by diltiazem and verapamil. Circ Res 1983;52:69I–76I.
29. Timmermans PBMWM, de Jonge A, van Meel JCA, Mathy MJ, van Zwreten PA. Influence of nifedipine on functional re-

sponses in vitro initiated at α_2-adrenoceptors. J Cardiovasc Pharmacol 1983;5:1–11.

30. Ruffolo RR, Morgan EL, Messick K. Possible relationship between receptor reserve and the differential antagonism of alpha-1 and alpha-2 adrenoceptor-mediated pressor responses by calcium channel antagonists in the pithed rat. J Pharmacol Exp Ther 1984;3:587–94.
31. Hall JE, Granger JP, Hester RL, Coleman TG, Smith MJ Jr, Cross RB. Mechanisms of escape from sodium retention during angiotensin II hypertension. Am J Physiol 1984;246:F627–34.
32. Rubenstein EB, Escalantec. Hypertensive crisis. Crit Care Clin 1989;5:477–95.
33. Bruckner R, Scholz H. Effects of α-adrenoceptor stimulation with phenylephrine in the presence of propranolol on force of contraction, slow-inward current, and cyclic AMP content in the bovine heart. Br J Pharmacol 1984;82:223–32.
34. Ask JA, Stene-Lansen G. Functional alpha-1-adrenoceptors in rat heart during beta-receptor blockade. Acta Physiol Scand 1984;120:633–9.
35. Hayes JS, Pollock GD, Fuller RW. In vivo cardiovascular responses to isoproterenol, dopamine, and tyramine after prolonged infusion of isoproterenol. J Pharmacol Exp Ther 1984;231:633–9.
36. Gaide MS, Wiggins JR, Fitterman WS, Cameron JS, Myerberg RJ, Bassett AL. Implications of altered inotropic effects of phenylephrine in pressure-overloaded cat ventricular muscle. J Cardiovasc Pharmacol 1984;6:238–43.
37. Gristwood R, Ginsberg R, Zers P. Are alpha-adrenoceptors coupled to contraction in human heart? Circulation 1986;74:II-374.
38. Goldstein DS. Arterial baroreflex sensitivity, plasma catecholamines, and pressor responsiveness in essential hypertension. Circulation 1983;68:234–40.
39. Buhler FR, Amann FW, Bolli P, et al. Elevated adrenaline and increased α-adrenoceptor mediated vasoconstriction in essential hypertension. J Cardiovasc Pharmacol 1982;4:S134–8.
40. Palmer GJ, Ziegler MG, Lake CR. Response to norepinephrine and blood pressure to stress increases with age. J Gerontol 1978;33:482–7.
41. Young JB, Rowe JW, Pallotta JA, Sparrow D, Landsberg L. Enhanced plasma norepinephrine response to upright posture and oral glucose administration in elderly human subjects. Metabolism 1980;29:532–9.
42. Seyde WC, Durieux ME, Longnecker DE. The hemodynamic response to isoflurane is altered in genetically hypertensive (SHR), as compared with normotensive (WKY), rats. Anesthesiology 1987;66:798–804.
43. Wilder J. Modern psychophysiology and the law of initial value. Am J Psychother 1958;12:199–221.
44. Blaise GA, Girard DC, Caille G, Hollman C, Buluran J, Meloche R. Is isoflurane a calcium antagonist? Ann Fr Anesth Reanim 1989;8:42–5.

Human Auditory Steady-State Response During General Anesthesia

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PLOURDE G, PICTON TW. Human auditory steady-state response during general anesthesia. Anesth Analg 1990; 71:460–8.

The 40-Hz auditory steady-state evoked response (ASSR) is a sinusoidal electrical response of the brain to periodically presented auditory stimuli. It was recorded during anesthesia in 10 elective surgical patients to evaluate its usefulness as a measure of the level of consciousness. The anesthetic agents used were thiopental, fentanyl, and isoflurane with or without nitrous oxide. Recordings were carried out during the period before induction and during induction, surgical anesthesia, emergence, and recovery from anesthesia. The level of consciousness was measured with an auditory stimulus detection task. The electroencephalogram (EEG) was also recorded for comparison with the ASSR. The following indices were analyzed: total EEG power, relative power in the β, α, θ, and δ frequency bands, and the median and spectral edge frequency. The amplitude of the ASSR was reduced significantly at the end of the induction period and decreased below noise levels during surgical anesthesia. It increased significantly during emergence and recovery. The amplitude during recovery remained significantly smaller than the preinduction values. The changes of the ASSR paralleled those of the level of consciousness. The EEG measurements were distorted by the presence of muscle artifacts that were prominent during emergence and recovery. The amplitude of the ASSR appears to provide a more reliable indicator of the level of consciousness than the EEG.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—isoflurane. ANESTHETICS, INTRAVENOUS—thiopental. BRAIN, EVOKED RESPONSES. MONITORING, ELECTROENCEPHALOGRAPHY—auditory evoked potentials.

The assessment of the level of consciousness is an important aspect in determining the level of anesthesia (1). The ability to respond to verbal commands is commonly used to assess the level of consciousness. Muscle relaxants unfortunately interfere with this assessment (2). There is, therefore, a great need for a physiological measurement that is affected by the level of consciousness but not by muscle relaxants.

Monitoring with the scalp-recorded electroencephalogram (EEG) offers a possible solution. However, anesthetic agents produce EEG patterns that are specific to the agent (and its dose) rather than to the level of anesthesia (3–6). Furthermore, the EEG rarely provides direct information on the level of consciousness (7).

The auditory steady-state response (ASSR) (8–10) is a sinusoidal electrical response of the brain to periodically presented auditory stimuli. It appears when the rate of stimulus delivery is sufficiently rapid to produce overlapping of the responses to individual stimuli. This response is most prominent for stimulus rates near 40 Hz (8).

Several features of the ASSR make it a possible candidate for use in monitoring the level of consciousness during anesthesia. The ASSR is a steady-state equivalent of the transient middle latency response (8) that shows graded, dose-related amplitude reduction with general anesthetics (11). The amplitude of the ASSR is reduced by 50% during sleep (12,13). Studies of normal subjects (14) have shown spontaneous amplitude fluctuations that apparently relate to concomitant fluctuations in alertness. Preliminary results have indicated that the amplitude of the ASSR is substantially reduced during general anesthesia (15).

Supported by a grant from the Medical Research Council (T.W.P.) and by a fellowship from the Fonds de la Recherche en Santé du Québec (G.P.).

Presented in part at a meeting of the Canadian Anaesthetists' Society in Ottawa, Canada, June 1989.

Received from the Human Neurosciences Research Unit, University of Ottawa, Ottawa, Ontario, Canada. Accepted for publication July 11, 1990.

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Any effective monitor of consciousness during general anesthesia must meet several criteria. First, the measurement must be readily and consistently obtained in nonanesthetized subjects. Second, it should not be significantly affected by anything other than changes in a subject's level of consciousness. Third, it must be clearly and consistently affected by anesthesia. Fourth, the anesthetic effects should be similar for different anesthetic agents. Fifth, the measurement must consistently return to normal values when the anesthetic is stopped and the patient regains consciousness.

We evaluated the ASSR in light of these criteria. Recordings were obtained in 10 normal subjects and in 10 patients undergoing general anesthesia. Our aim for this initial investigation was to relate the ASSR and the level of consciousness, which was measured with an auditory signal detection task. The EEG, which is an accepted method for monitoring the level of anesthesia, was also recorded for comparison with the ASSR.

Methods

Subjects

The project was approved by the Institutional Research Ethics Committee. Written informed consent was obtained from all participants. Ten unanesthetized subjects (seven men) participated in the initial control portion of the study. The mean age was 31 yr (range, 23–43). They were tested in a sound-attenuated, electrically shielded room. Ten patients (six women) (ASA I or II) were then tested during elective surgery. The mean age was 34 yr (range, 21–61). Surgical procedures consisted of plastic surgery (six patients), orthopedic surgery (two patients), urologic surgery (one patient), and general surgery (one patient).

There was no history of neurologic or otologic disease in the participants.

Anesthetic Technique

Eight patients were premedicated with diazepam (0.1 mg/kg) by mouth 60–90 min preoperatively. Two patients received no premedication. Anesthesia was induced with thiopental (5 mg/kg), injected in 1 min. After failure to open eyes on command, vecuronium (0.1 mg/kg) was used to facilitate tracheal intubation. The lungs were mechanically ventilated to maintain the end-tidal carbon dioxide (CO_2) partial pressure at 30 mm Hg (mass spectrometry). Fentanyl (3 μg/kg before skin incision) and isoflurane (0.5%–1.5% end-tidal) in oxygen (O_2) (five patients) or in nitrous oxide (N_2O) (60% end-tidal)/O_2 (five patients) were used for maintenance of anesthesia. The nasopharyngeal temperature was continuously monitored. Neostigmine (with glycopyrrolate) was used to cause a full reversal of muscular paralysis 10 min before emergence.

Auditory Steady-State Responses

Stimuli. Tonebursts (500 Hz, 15-ms duration, 5-ms rise/fall time, 90-dB peak sound pressure level) were presented binaurally at a rate of 40 per second via TDH-49 earphones in the controls and via insert earphones (Etymotic Research, model ER3A) in the surgical patients. The frequency was occasionally (10 per minute on average with random timing) increased to 700 Hz for 75 ms to produce "target" stimuli, to which the patients were required to respond by pressing a button if they perceived them. The percentage of detected targets (i.e., those responded to by a button press) was used as an index of the level of responsiveness.

Recording. The EEG was recorded with gold-plated cup electrodes attached with saline gel and collodion. The interelectrode impedances were less than 5 kΩ (10 Hz). Three electrodes were placed according to the International 10–20 system (16) at frontal (Fz), central (Cz), and parietal (Pz) midsagittal scalp locations with the right mastoid (M2) as common reference. Vertical eye movements (EOG) (forehead-cheek) were also recorded to allow rejection of epochs contaminated by eye movements. Half-amplitude lower and upper cutoffs were 0.16 and 100 Hz with a −20 dB per decade roll-off. The amplifiers followed the EEG convention that negativity at the scalp relative to the reference was plotted upward.

The duration of the analog-to-digital epoch was 1490 ms. The sampling frequency was 688 Hz per channel. The interval between onset of epochs was 2000 ms. The analog-to-digital resolution was 12 bits. Epochs contaminated by excessive muscle or eye movements were rejected. The rejection level on all channels for the control subjects was ±87.5 μV and for the anesthetized patients ±175 μV. (Less stringent rejection criteria were used with the anesthetized patients because of the high amplitude of the EEG during anesthesia.) For each recording, 50 epochs (100 s) were averaged.

Measurements. The responses were analyzed using the fast Fourier transform (17, 18) of the unfiltered averaged traces.

Auditory Brainstem Response

Conductive hearing loss attenuates the ASSR. Auditory brainstem responses were therefore recorded before anesthesia and during surgery in three patients to rule out significant conductive hearing loss as a possible cause of the attenuation of the ASSR during anesthesia.

Stimuli. Rarefaction clicks with an intensity of 95-dB peak sound pressure level (equivalent to 60 dB above normal threshold) and a duration of 0.1 ms were presented monaurally at a rate of 11.1 per second.

Recording. The recordings were from Cz-left mastoid (M1) and Cz-right mastoid (M2). The recording technique conformed to current recommendations (19). Both ears were evaluated with at least three averages of 2000 epochs. Replicate waveforms were combined and digitally filtered (50–2500 Hz) before measurements.

Measurements. Waves I, II, and V were identified on the Cz-ipsilateral mastoid channel according to current clinical procedures (19). The amplitudes were measured relative to the most negative succeeding peak or inflection within the next 1.5 ms.

Electroencephalogram

Recording. The EEG was recorded for 8 s after every other ASSR recording. Recording parameters were otherwise similar to those used for the ASSR. Because of time constraints, the EEG for induction was recorded only during late induction.

Measurements. The following measures were derived from the power spectrum: median (20) and spectral edge (21) (95% quantile frequency) as well as the average power in the δ (0.5–3.4 Hz), θ (3.5–7.4 Hz), α (7.5–13.4 Hz), and β (13.5–30.0 Hz) frequency bands expressed as percentage of total power from 0.5 to 30.0 Hz. Determination of the median and 95% quantile frequencies was done after filtering the EEG from 0.5 to 32 Hz in accordance with current anesthetic practice. The ratio $(\alpha + \beta)/(\delta + \theta)$ was also computed.

Design

Awake control subjects were initially tested to ensure that consistent responses could be obtained with the experimental protocol. There were two recordings for each control subject. The recordings for each subject were combined before measurement. With anesthetized patients recordings were obtained during the following periods: preinduction (30–90 min before induction), induction, surgery, emergence, and recovery. Both control subjects and patients kept their eyes closed and were instructed to press a button after each target whenever possible. The injection of thiopental began 30 s after the beginning of the early induction recording and lasted 1 min. The late induction recording immediately followed the early induction recording. The recordings during surgery were done at stable (over 10 min) concentrations of isoflurane: 0.5% end tidal when administered with 60% N_2O and 1.15% end tidal when administered in O_2 alone. To obtain preliminary dose-response information, recordings were obtained before emergence with three patients at 0.5% end-tidal (stable over 10 min) isoflurane in O_2. After surgery, the trachea was extubated as soon as the patients were able to open their eyes on command. Emergence was defined as the 10-min period immediately after the return of the ability to open the eyes on command and was followed by recovery. Within each period other than induction multiple recordings were combined before evaluation. The effect of surgical stimulation was not evaluated because of cautery interference after skin incision. Recordings could not be obtained from all patients in all periods because of factors such as movement and shivering that caused epochs to be rejected.

Statistical Analysis

The Rayleigh test for phase coherence and Hotelling's T^2 statistic (22) were used to determine if the response could be reliably distinguished from background noise. This was done separately for the control awake subjects and for the anesthetized patients.

The results were analyzed with one-way (awake controls) and two-way analyses of variance for repeated measures using the Geisser–Greenhouse adjustment of the significance levels (23,24). The analyses of variance for the anesthetized patients were also corrected for the substitution of missing values (23). The grouping factor for the two-way analyses of variance was presence or absence of N_2O. Paired *t*-tests were used for comparisons in the patients. The criterion for significance was $P < 0.05$ for the analyses of variance and $P < 0.01$ for the paired comparisons

Table 1. Target Stimuli Detection

Period	n	Percentage of detected targets	Range
Preinduction	10	99 ± 1	97–100
Induction (early)	7	77 ± 22	33–100
Induction (late)	7	2 ± 1	0–4
Surgery[a]	—	—	—
Emergence	8	11 ± 10	0–34
Recovery	9	64 ± 11	42–89
ANOVA		$P < 0.001$	

ANOVA, analysis of variance.

Percentage of detected targets is given as mean ± SD.

[a] During surgery, responsiveness to the target was not assessed because of muscle paralysis and inability to hold the button-press switch.

to reduce the likelihood of spurious significance due to multiple comparisons.

Results

Awake Control Subjects

The mean amplitude of the ASSR was 0.48 μV (SD, 0.10). Phase coherence and Hotelling's T^2 statistic showed that the responses were clearly distinguishable from background noise ($P < 0.01$).

Anesthetized Patients

Anesthetic management. The average interval between induction and extubation was 126 min (SD, 56). The recordings in the recovery room were started on average 38 min (SD, 23; range, 10–65) after extubation and were completed 68 min (SD, 31; range, 27–114) after extubation.

The mean nasopharyngeal temperature during surgery was 36.2°C (SD, 0.51; range, 35.4–37.0). The mean end-tidal partial pressure of CO_2 during surgery was 29.3 mm Hg (SD, 2.0; range, 27.1–32.3). For patients receiving isoflurane and N_2O, the mean end-tidal concentrations were respectively 0.57% (SD, 0.12) and 61% (SD, 8). For patients receiving isoflurane only, the mean end-tidal level was 1.04% (SD, 0.08). The level of anesthesia was judged clinically adequate during the surgical recordings. There was no tachycardia, hypertension, or sudation.

Detection of target stimuli. The percentage of target stimuli responded to by the patients is shown in Table 1. There were significant differences between the recording periods (analysis of variance, $P < 0.001$). The following differences were significant ($P < 0.01$). The preinduction value exceeded late induction, emergence, and recovery values. The early induction value exceeded late induction and emergence values. The recovery value exceeded late induction and emergence values, but was inferior to the preinduction value.

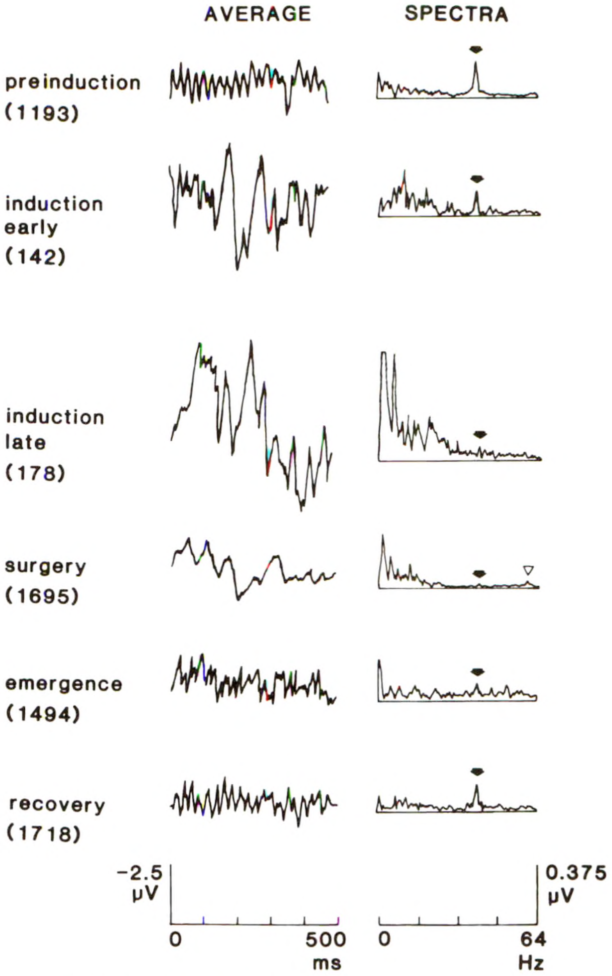

Figure 1. Average unfiltered waveforms (*left*) recorded from Cz for anesthetized patients and corresponding amplitude spectra (*right*) for each period. The amplitude spectra were obtained by fast Fourier transform. The number of epochs included in the average waveforms is given in *parentheses* below each period. The amplitude peaks at 40 Hz are indicated by the *arrows*. The *open triangle* shows power line artifact (60 Hz). For simplicity, only the initial portions of the average waveforms and of the spectra are shown.

Steady-state responses. The average ASSR waveforms for all patients and the amplitude spectra are shown in Figure 1. The amplitude spectra revealed a clearly recognizable peak at 40 Hz relative to adjacent frequencies during preinduction, early induction, and recovery. During late induction and emergence, the 40-Hz activity was reduced and not clearly distinguishable from background noise, which is particularly high during these periods. Although there was

Table 2. Auditory Steady-State Responses

Period	n	Amplitude (μV)
Preinduction	10	0.41 ± 0.13
Induction (early)	7	0.40 ± 0.12
Induction (late)	7	0.17 ± 0.11
Surgery	10	0.03 ± 0.01
Emergence	8	0.13 ± 0.09
Recovery	9	0.24 ± 0.07
ANOVA (main effect)		$P < 0.001$

ANOVA, analysis of variance.
Amplitude values are given as mean ± SD.

Table 3. Auditory Brainstem Responses

	Preinduction		Surgery	
Wave	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
I	1.85	0.15	1.92	0.20
III	3.97	0.15	4.20	0.22
V	6.01	0.51	6.38	0.33

Values are given as mean value for three patients.
Right and left side collapsed.

Table 4. Electroencephalogram (EEG)—Power and Quantile Frequencies

Period	n	EEG power (μV^2)	Median frequency (Hz)	95% Quantile frequency (Hz)
Preinduction	10	2.7 ± 5.6	6.0 ± 3.5	20.2 ± 6.1
Induction	7	23.1 ± 14.7	4.7 ± 3.9	13.5 ± 6.0
Surgery	10	4.8 ± 1.2	3.9 ± 2.5	13.4 ± 4.5
Emergence	8	1.7 ± 0.7	11.3 ± 4.6	28.2 ± 1.4
Recovery	9	0.7 ± 0.2	8.1 ± 3.8	27.8 ± 1.7
ANOVA (main effect)		$P < 0.001$	$P < 0.001$	$P < 0.001$

ANOVA, analysis of variance.
All values, with the exception of n are given as mean ± SD.

some 40-Hz activity during surgery, it was not clearly distinguishable from the adjacent frequencies. The high-frequency peak during surgery (open triangle) was faster than 40 Hz and largely due to power line artifact (60 Hz).

The measurements from individual patients are summarized in Table 2. Results of the analyses of variance yielded significant main effects of the period on amplitude ($P < 0.001$). There were no significant effects due to N_2O and no interactions.

The amplitude of the ASSR was reduced by more than 50% during late induction ($P < 0.01$) compared with preinduction. There was a profound amplitude reduction during surgery compared with preinduction ($P < 0.01$). The amplitude during late induction and emergence was larger than during surgery ($0.01 < P < 0.05$). There was a significant amplitude increase during recovery compared with emergence ($P < 0.01$), although the amplitude during recovery remained significantly smaller than during preinduction ($P < 0.01$). The changes in the amplitude of the 40-Hz peak paralleled those in the percentage of detected targets (Table 1).

Phase coherence and Hotelling's T^2 statistic indicated that the responses were significantly different from background noise ($P < 0.01$) during preinduction, early induction, and recovery. Borderline values ($0.05 < P < 0.10$) were obtained for late induction and emergence. No consistent response was present during surgery ($P = 0.2$).

In two patients in whom tracheal intubation was delayed for 3–4 min, the effects of thiopental alone were studied. The ASSR amplitude decreased to a level comparable to surgical recordings. The response was smaller than 0.06 μV and there was no recognizable 40-Hz peak in the spectrum. There was a fair amount of high-frequency activity in the recording.

In three patients of the isoflurane-only group, the ASSR was recorded before emergence at stable (over 10 min) end-tidal concentration of isoflurane of 0.5%. The amplitudes were 0.02, 0.03, and 0.03 μV. These are comparable to those obtained during surgery.

Brainstem responses. The results are presented in Table 3. The latency of wave I was increased during surgery by 0.07 ms. Waves III and V were delayed by 0.23 and 0.37 ms, respectively. The amplitudes of waves I and III were slightly increased whereas the amplitude of wave V was decreased. The mean ASSR amplitude for these three patients was 0.44 μV preoperatively and 0.05 during surgery.

Electroencephalogram. The results are presented in Tables 4 and 5. The analysis of variance showed a significant ($P < 0.001$) period effect for EEG power, relative β power, and median and spectral edge frequency. The analysis of variance for the ratio $(\alpha + \beta)/(\delta + \theta)$ was also significant ($P < 0.01$). There were no effects due to N_2O and no interactions.

There was a significant increase in total EEG power after induction ($P < 0.01$ compared with preinduction). Total power returned toward baseline during surgery.

β Activity decreased significantly during surgery ($P < 0.01$ compared with preinduction). It increased significantly during emergence ($P < 0.001$ compared with surgery). It remained high during recovery ($P <$

Table 5. Electroencephalogram (EEG)—Relative Power

Period	δ (0.5–3.4 Hz)	θ (3.5–7.4 Hz)	α (7.4–13.4 Hz)	β (13.4–30 Hz)	$(\alpha + \beta)/(\delta + \theta)$
Preinduction	0.53 ± 0.23	0.20 ± 0.14	0.21 ± 0.14	0.06 ± 0.04	0.37 ± 0.26
Induction	0.66 ± 0.17	0.19 ± 0.10	0.12 ± 0.13	0.03 ± 0.04	0.23 ± 0.27
Surgery	0.64 ± 0.15	0.18 ± 0.05	0.16 ± 0.12	0.02 ± 0.02	0.26 ± 0.23
Emergence	0.42 ± 0.13	0.19 ± 0.07	0.23 ± 0.08	0.16 ± 0.09	0.72 ± 0.38
Recovery	0.54 ± 0.21	0.15 ± 0.07	0.20 ± 0.13	0.11 ± 0.04	0.54 ± 0.37
ANOVA (main effect)	NS	NS	NS	$P < 0.001$	$P < 0.01$

ANOVA, analysis of variance; NS, not significant.
Values are given as mean ± SD.

0.01 compared with preinduction). The median frequency showed similar changes except that there was no difference between preinduction and recovery. The ratio $(\alpha + \beta)/(\theta + \delta)$ increased significantly ($P < 0.01$) from surgery to emergence.

The spectral edge frequency decreased after induction ($P < 0.01$) and remained at that same level during surgery. During emergence it increased ($P < 0.01$ compared with surgery) even above preinduction values ($P < 0.01$). There was no change from emergence to recovery.

The unfiltered EEG segments (Cz) and power spectra from a representative patient are shown in Figure 2. End-tidal concentrations of N_2O and isoflurane were 60% and 0.5%, respectively. α Activity and δ activity predominated preoperatively. During induction there was a large increase in EEG power particularly in the δ and θ bands. During surgery, δ activity predominated with some superimposed α activity. During emergence there was a reduction of δ activity. During recovery, the spectrum showed low levels of activity across the spectrum with δ and θ activity predominant. Muscle artifacts are evident in the EEG segments during emergence and recovery.

Discussion

The ASSR was consistently recorded in normal waking subjects and in patients before anesthesia. This study demonstrated that the amplitude of the 40-Hz ASSR is reduced to 5%–15% of control values during general anesthesia with isoflurane or isoflurane/N_2O. The findings replicate the observations by Hogan (15) who described a 78% amplitude reduction of the averaged ASSR during isoflurane/N_2O anesthesia. At comparable end-tidal levels, Heneghan et al. (25) described about a 50% reduction of the amplitude of the transient middle-latency auditory evoked response during anesthesia with isoflurane and N_2O. Most anesthetic agents increase the latency and reduce the amplitude of the transient middle-latency auditory response (11,26,27). This will interfere with the formation of the ASSR, which depends in part on the overlapping of the response to successive stimuli. The ASSR is therefore more susceptible to anesthesia than the transient response.

The attenuation of the ASSR cannot be accounted for by conductive hearing loss because the auditory brainstem response, concomitantly recorded in three patients, showed no evidence of a substantial increase in wave I latency. Conductive hearing loss is virtually always associated with increased wave I latency (28). The 0.07-ms prolongation of wave I latency found in our patients would correspond to only 2-dB attenuation of stimulus intensity (28). The latencies of waves III and V were slightly prolonged, as expected during isoflurane anesthesia (25,29).

The ASSR became attenuated during late induction. The injection of thiopental was completed at that time, and no other drug had been given except vecuronium. Therefore, thiopental alone can attenuate the ASSR. In two patients the effect of thiopental alone was studied for a longer period, because tracheal intubation was delayed by 3–4 min. The ASSR amplitude was comparable to that measured during isoflurane anesthesia 30–90 min later. Because of rapid redistribution, the residual effects of thiopental during surgery may be assumed to be negligible. Thus, the change in the ASSR seen with thiopental or isoflurane is similar, suggesting that the change is not agent-specific.

Furthermore, the attenuation of the ASSR does not appear to be dose-dependent. Recordings in three patients at 0.5% end-tidal isoflurane were similar to those obtained during surgery (1.0% end-tidal isoflurane). This contrasts with the dose-dependent effects of isoflurane on the transient middle-latency auditory response (25). The amplitude of the ASSR may there-

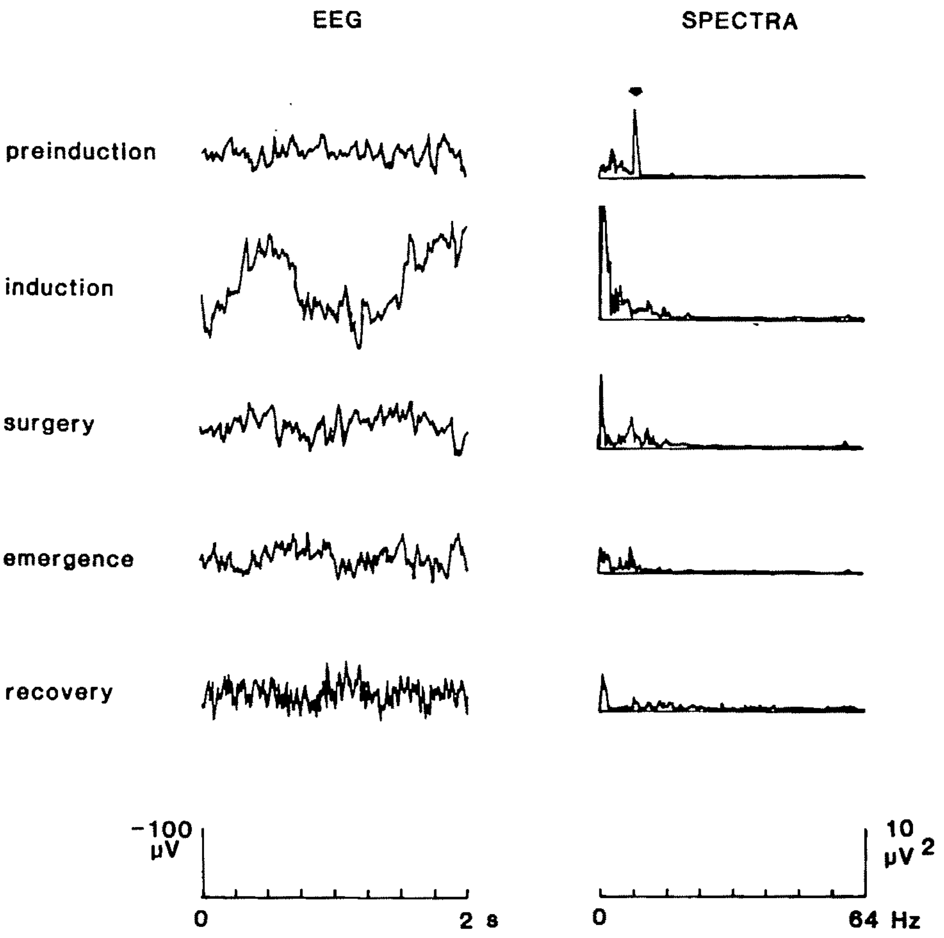

Figure 2. Electroencephalogram recorded from Cz for one representative patient. The patient received N_2O (60% end-tidal) and isoflurane (0.5% end-tidal). On the *left* is shown a brief portion (2 s) of the EEG for each period. On the *right* is shown the spectrum obtained with the fast Fourier transform of 8 s of EEG. Preinduction α activity is denoted by the *arrow*. Low frequency power has been clipped during induction.

fore be related more to the level of consciousness than to the level of the anesthetic agent.

The ASSR was clearly recognizable during emergence and recovery. However, it was significantly smaller than during the preanesthetic period, having about one-third the amplitude in emergence and just over half the amplitude in recovery. The patients were not fully alert during these periods. The behavioral responsiveness to the occasional target tones (Table 1) was quite reduced. It is possible, therefore, that the ASSR reflects the decreased level of arousal or wakefulness—somewhere between sleep and alertness. Sleep is generally associated with a reduction of the ASSR to about one-half to one-third its normal waking amplitude (12,13).

Two limitations must be emphasized. First, the absence of behavioral responsiveness to target stimuli during surgery means nothing because muscle paralysis renders button-pressing impossible. We therefore did not obtain a valid behavioral measure during surgery. Second, we are not contending that the ASSR is a monitor of intraoperative awareness or recall thereof. The ASSR appears to reflect the level of wakefulness. Awareness and wakefulness can be dissociated in both normal subjects and neurologic patients. A normal subject can be awake but unaware of certain aspects of his or her environment. A neuro-vegetative patient can be awake but totally unaware and devoid of any cognitive activity (30). Awareness therefore implies more than wakefulness.

The increased EEG power after induction is consistent with the known effects of thiopental (4,5). Of all the EEG parameters, it is the spectral edge frequency that showed the most appropriate changes with the various stages of anesthesia. There was a significant decrease after induction, one that persisted during surgery. However, the spectral edge frequency reached values *above* control during emergence and recovery. In all likelihood, contamination by muscle artifacts accounts for this increase of the spectral edge frequency during emergence and recovery. There is overlap between the power spectrum of the EEG and of the muscle activity (31). Muscle artifacts may also account for the increase of the median frequency and of the activity in the β band from surgery to emergence. Muscle artifacts complicate interpretation of the EEG and may easily invalidate procedures that attempt to summarize EEG data as a single number. The importance of muscle artifacts is frequently overlooked because many EEG and evoked-potential studies focus primarily on preanesthetic, postinduction, and surgical stages. Furthermore, the muscle artifacts are frequently masked because the spectral waveforms are smoothed before display (5). Because emergence from anesthesia is frequently associated with increased muscle activity (e.g., shivering, limb movements), complete elimination of muscle artifacts is difficult. In paralyzed patients, EEG changes from surgical anesthesia to emergence would be different because muscle artifacts would not occur. It is very difficult to determine whether the EEG changes in fully paralyzed patients emerging from anesthesia would relate to the regaining of consciousness. We have recorded the EEG only from midline scalp locations in contrast to the usual choice of lateral scalp locations for monitoring during anesthesia. This does not invalidate our recordings, however, because anesthetic-induced EEG changes are widespread (in contrast to ischemic changes, which may be limited to one hemisphere).

Our recording techniques allowed us to record both the ASSR and the transient responses to the targets. The transient responses will be reported in another paper. If one wishes just to record the ASSR, several procedures can be used to improve the detection of the response (32). The most important would be to increase the duration of the recording epoch. Another would be to stimulate each ear separately using different stimulus rates.

We conclude that the ASSR is a promising tool for monitoring anesthesia. It is consistently recorded in normal subjects and consistently attenuated by anesthesia. This attenuation by general anesthesia seems related to a decreased level of consciousness and does not appear to be agent-specific or dose-dependent. The ASSR appears particularly useful in studying the transition from consciousness to unconsciousness as well as the recovery from anesthesia. The ASSR is relatively easy to measure and is less influenced by muscle artifacts than is the EEG.

Adrian Kellett and Dick Mowrey provided essential technical and programming support, respectively. Members of the Royal Victoria Hospital Anesthesia Department made every effort to provide optimal working conditions. Liam Claffey and Pascal Labrecque provided helpful comments during the writing of the manuscript. Susan Caney provided expert secretarial assistance.

References

1. Grantham CD, Hameroff SR. Monitoring anesthetic depth. In: Blitt CD, ed. Monitoring in anesthesia and critical care medicine. New York: Churchill Livingstone, 1985:427–40.
2. Evans JM. Clinical signs and autonomic responses. In: Rosen M, Lunn JN, ed. Consciousness, awareness and pain in general anesthesia. London: Butterworths, 1987:18–33.
3. Levy WJ, Shapiro HM, Maruchak G, Meathe E. Automated EEG processing for intra-operative monitoring: a comparison of techniques. Anesthesiology 1980;53:223–36.
4. Clark DL, Rosner BS. Neurophysiologic effects of general anesthetics. I. The electroencephalogram and sensory evoked responses in man. Anesthesiology 1973;38:564–82.
5. Stockard J, Bickford R. The neurophysiology of anaesthesia. In: Gordon E, ed. A basis and practice of neuroanesthesia. Amsterdam: North Holland Biomedical Press, 1981:3–46.
6. Pichlmayr I, Lips U, Künkel H. The electroencephalogram in anesthesia. Berlin: Springer-Verlag, 1984.
7. Mori K. The EEG and awareness during anaesthesia (editorial). Anaesthesia 1987;42:1153–5.
8. Galambos R, Makeig S, Talmachoff PJ. A 40 Hz auditory potential recorded from the human scalp. Proc Natl Acad Sci USA 1981;78:2643–7.
9. Stapells DR, Linden D, Suffield JB, Hamel G, Picton TW. Human auditory steady-state potentials. Ear Hear 1984;5:105–13.
10. Picton TW. Human auditory steady state responses. In: Barber C, Blum T, eds. Evoked potentials III. London: Butterworths, 1987:117–23.
11. Jones JG. Use of evoked responses in the EEG to measure depth of anesthesia. In: Rosen M, Lunn JN, eds. Consciousness, awareness and pain in general anesthesia. London: Butterworths, 1987:99–111.
12. Linden RD, Campbell KB, Hamel G, Picton TW. Human auditory steady state evoked potentials during sleep. Ear Hear 1985;6:167–74.
13. Jerger J, Chmiel R, Frost JD, Coker N. Effect of sleep on the auditory steady state evoked potential. Ear Hear 1986;7:240–5.
14. Galambos R, Makeig S. Dynamic changes in steady-state responses. In: Basar E, ed. Dynamics of sensory and cognitive processing by the brain. Berlin: Springer-Verlag, 1988:103–22.
15. Hogan K. 40 Hz steady-state evoked potentials (SSEP) during isoflurane-N_2O anesthesia (abstract). Anesthesiology 1987;67: A402.
16. Jasper HH. The ten-twenty electrode system of the International Federation. Electroenceph Clin Neurophysiol 1958;10: 371–5.
17. Beauchamp K, Yuen C. Digital methods for signal analysis. London: Allen and Unvin, 1979.
18. Picton TW, Hink RF, Perez-Abalo M, Linden RD, Wiens AS. Evoked potentials: how now? J Electrophysiol Tech 1984;10: 177–221.

19. American Electroencephalographic Society. Guidelines for clinical evoked potential studies. J Clin Neurophysiol 1984;1:3–53.
20. Stoeckel H, Schwilden H. Median EEG frequency. In: Rosen M, Lunn JN, eds. Consciousness, awareness and pain in general anesthesia. London: Butterworths, 1987:53–60.
21. Rampil IJ, Matteo RS. Changes in EEG spectral edge frequency correlate with the hemodynamic response to laryngoscopy and intubation. Anesthesiology 1987;67:139–41.
22. Picton TW, Vasjar J, Rodriguez R, Campbell KB. Reliability estimates for steady-state evoked potentials. Electroencephalogr Clin Neurophysiol 1987;68:119–31.
23. Kirk RE. Experimental design—procedures for the behavioral sciences. 2nd ed. Monterrey, Calif.: Brooks/Cole, 1982.
24. Dixon WJ, ed. BMDP statistical software. Los Angeles: University of California Press, 1985.
25. Heneghan CPH, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. Br J Anaesth 1987;59:277–82.
26. Madler Ch, Pöppel E. Auditory evoked potentials indicate the loss of neuronal oscillations during general anesthesia. Naturwissenschaften 1987;74:42–3.
27. Goff WR, Allison T, Lyons W, Fisher TC, Conte R. Origin of short latency auditory evoked potentials in man. In: Desmedt JE, ed. Progress in clinical neurophysiology: auditory evoked potentials in man. Basel: Karger, 1977:30–44.
28. Chiappa KH. Evoked potentials in clinical medicine. New York: Raven Press, 1985.
29. Manninen PH, Lam AM, Nicholas JF. The effects of isoflurane and isoflurane-nitrous oxide anesthesia on brainstem auditory evoked potentials in humans. Anesth Analg 1985;64:43–7.
30. Plum F, Posner JB. Stupor and coma. Philadelphia: FA Paris, 1982.
31. Bickford RG. Newer methods of recording and analyzing EEGs. In: Klass DW, Daly DD, eds. Current practice of clinical electroencephalography. New York: Raven Press, 1979;451–2.
32. Regan D. Human brain electrophysiology. Evoked potentials and evoked magnetic fields in science and medicine. New York: Elsevier, 1989.

ANESTH ANALG 1990;71:469–74

Does Isoflurane Lead to a Higher Incidence of Myocardial Infarction and Perioperative Death Than Enflurane in Coronary Artery Surgery?

A Clinical Study of 1178 Patients

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INOUE K, REICHELT W, EL-BANAYOSY A, MINAMI K, DALLMANN G, HARTMANN N, WINDELER J. Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? A clinical study of 1178 patients. Anesth Analg 1990;71:469–74.

To examine if the choice of volatile agents influences cardiac outcome in coronary artery surgery, 1178 patients undergoing elective coronary artery bypass grafting without additional operations received enflurane (608) or isoflurane (570) as their primary anesthetics. The inspired concentration of volatile agent (administered with 50% nitrous oxide) was adjusted depending on the level of blood pressure at the discretion of the anesthesiologist. In addition to the volatile agent assigned, each patient received small doses of fentanyl at induction and before sternotomy (total 0.006–0.008 mg/kg). The groups did not differ in preoperative and surgical characteristics except for a more frequent history of renal dysfunction in patients given isoflurane. The rates of postoperative myocardial infarction, administration of positive inotropic agents at the time of weaning from cardiopulmonary bypass, and in-hospital deaths in the enflurane and isoflurane groups were 1.8% and 4.0% ($P < 0.05$), 4.9% and 8.1% ($P < 0.05\%$), and 0.3% and 2.1% ($P < 0.01$), respectively. Although the mechanism of the adverse effects of isoflurane could not be clarified in this study, these results demonstrate that the use of isoflurane could be inappropriate in patients undergoing coronary artery bypass grafting.

Key Words: ANESTHESIA, CARDIAC—outcome. ANESTHETICS, VOLATILE—enflurane, isoflurane. SURGERY, CORONARY ARTERY BYPASS GRAFTING.

Recent laboratory as well as clinical studies have suggested that isoflurane should not be used in patients with coronary artery disease because it may produce myocardial ischemia by a coronary steal (1–4). In contrast, others have found no such deleterious effects of isoflurane (5,6). Furthermore, Tarnow et al. (7) reported the beneficial effects of isoflurane in pacing-induced ischemia. Thus, the question remains whether the use of isoflurane is appropriate in patients undergoing coronary artery bypass grafting (CABG). In view of this, we examined the effects of isoflurane and enflurane on cardiac outcome in coronary artery surgery in a large patient population.

Methods

With institutional ethical committee approval and informed consent, the use of primary anesthetic agent, isoflurane or enflurane, was alternated on a weekly basis in all operating rooms. One thousand one hundred seventy-eight patients undergoing elective CABG surgery were studied from February 27, 1987, to April 29, 1988. Excluded were patients who had any associated operation such as valve replacement, plication or resection of a ventricular aneurysm, and simultaneous carotid endarterectomy, as

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Presented in part at the Sixty-Fourth Congress of The International Anesthesia Research Society, Honolulu, Hawaii, March 1990.

Received from the Department of Anesthesiology and the Department of Thoracic and Cardiovascular Surgery, Heart Center Nordrhein-Westfalen, Bad Oeynhausen; and the Department of Medical Informatics and Biomathematics, Ruhr-University, Bochum, Federal Republic of Germany. Accepted for publication July 18, 1990.

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well as those who underwent internal mammary artery grafting. Preoperative risk factors were evaluated by calculating the Montreal Heart Institute Risk Classification Index (class 0 = normal risk; class 1 = increased risk; class 2 = high risk) (8).

Each patient was premedicated with oral lormetazepam and morphine sulfate intramuscularly approximately 1–1.5 h before induction of anesthesia. Anesthesia was usually induced with 1.5–2 mg/kg methohexital following 0.003–0.005 mg/kg fentanyl. Tracheal intubation was facilitated with succinylcholine. Before sternotomy, additional doses of fentanyl (total 0.006–0.008 mg/kg, including the induction dose) were administered. Anesthesia was maintained with the volatile agent assigned and nitrous oxide (50%) in oxygen. Vecuronium was used for muscle relaxation.

Hemodynamic monitoring included the direct measurement of arterial pressure and central venous pressure. Electrocardiograms (ECGs) were obtained from standard limb leads and V_5 lead.

The inspired concentration of volatile agent was adjusted depending on the level of blood pressure at the discretion of the anesthesiologist. If necessary, nitroglycerin and/or nifedipine were administered intravenously to treat hypertension. Hypotension during the prebypass period was treated by lightening the anesthetic level and by fluid administration and/or head-down position. Positive inotropic agents were used only rarely in the prebypass period. Systolic blood pressure was kept as far as possible between 110 and 90 mm Hg. Heart rates below 45 beats/min were treated with atropine. To lower heart rate, anesthesia was deepened and additional doses of fentanyl were administered. There was no standard protocol for the treatment of myocardial ischemia evidenced in the ECG but, in addition to treating hemodynamic abnormality if it existed, nitroglycerin infusion was tried in most cases.

In 1002 cases, distal anastomoses of vein grafts were performed without cardioplegia by clamping the aorta intermittently during systemic hypothermia, namely, cooling of blood in the extracorporeal circuit, after establishment of total bypass, to 27°C for at least 5 min. The aorta was then cross-clamped and one or two distal anastomoses made, which usually took less than 15 min with a fibrillating heart. During the period of cross-clamping, blood temperature was brought to 34°C to avoid excessive cooling of the body. Shortly before unclamping the aorta, blood was cooled again to 27°C to perfuse coronary arteries with cold blood. After unclamping, the coronary arteries were reperfused for at least 3 min until the next cross-clamping. In the remaining 176 cases, the aorta was cross-clamped during the whole period of distal anastomoses after the infusion of cold cardioplegic solution (4°–8°C). The use of cardioplegia depended entirely on the preference of the surgeon. Proximal aortic anastomoses were performed during rewarming after the cross-clamp was removed and the heart was defibrillated. During cardiopulmonary bypass (CPB), hypertension and hypotension were treated primarily by changing the concentration of volatile agent.

After CPB, the volatile agent assigned was administered in 100% oxygen. In case of difficult weaning from CPB, the anesthesia was switched to intravenous fentanyl and midazolam. When positive inotropic agents were required, dopamine or dopamine with epinephrine was administered.

The postoperative care of patients in the intensive care unit (ICU) was done by physicians from the surgical department. The patients were usually mechanically ventilated for 2–3 h postoperatively. Unless their clinical status did not permit, patients were transferred from the ICU to a regular ward on the morning of the first postoperative day.

Blood samples were taken from all patients for measurement of plasma levels of creatine kinase (CK) and CK-MB on the morning of the first postoperative day. Total CK activity was determined by incubation at 25°C using the standard method recommended by the German Society of Clinical Chemistry (9). CK-MB was measured with an immunoinhibition method (10). A 12-lead ECG was recorded routinely, postoperatively on arrival of the patient in the ICU, on the morning of the first postoperative day, and 1 day before discharge from the hospital. Patients were usually discharged between the fourth and 10th postoperative days.

Myocardial infarction (MI) was considered present when new Q waves (>0.04 s) appeared, and when CK-MB was in excess of 40 U/L. Diagnosis of MI required that both criteria be met. In the case of death, results of autopsy were used in the diagnosis of MI. In one patient who died immediately after arrival in the ICU, the diagnosis of MI was made only from the ECG. For analysis of mortality, only those patients who died in the hospital were included.

Mean values were compared by Student's *t*-test for unpaired data. Frequency data were tested by χ^2-analysis (in some data by Fisher's exact test). In addition, multivariate discriminant analysis was used to find factors other than the choice of anesthetics that influenced MI frequency and mortality because we chose a nonrandom method of allocation of patients to the two anesthetic groups (alternate weekly schedule) and because, at the time of statistical anal-

Table 1. Preoperative Patient Characteristics

	Enflurane (*n* = 608)	Isoflurane (*n* = 570)	*P*
Age (yr)	59.2 ± 8.6	59.5 ±9.1	0.69
Female	16.3	17.9	0.46
Body mass index[a]	25.3 ± 2.4	25.1 ± 2.5	0.17
Preoperative medication			
Digitalis	11.0	13.3	0.22
β-Blocker	39.5	41.9	0.39
Calcium antagonist	84.7	87.4	0.18
Nitrate	85.0	85.1	0.97
Antihypertensive	3.0	3.0	0.98
Diuretic	16.0	18.1	0.33
Antiarrhythmic	7.1	7.9	0.59
History of MI			0.77
None	38.3	37.2	
>3 mo	51.3	54.0	
<3 mo	8.9	7.7	
<3 wk	1.5	1.1	
Risk factors (MHI)			0.25
Normal (0)	37.7	33.9	
Increased (1)	43.3	47.4	
High (2)	19.1	18.8	
Left main disease	7.9	7.7	0.91
Obesity	2.6	2.5	0.84
Age >70 yr	10.0	10.2	0.93
Diabetes	11.8	11.9	0.96
Reoperation	2.5	3.3	0.34
Renal dysfunction	4.9	8.4	0.016

MI, myocardial infarction; MHI, Montreal Heart Institute Classification; obesity, body mass index > 30.

All values are expressed as percentage, except for age and body mass index, which are expressed as mean ± SD.

[a] Body mass index = weight/height^2 (kg/m^2).

Table 2. Assignment of Surgeons (No. of Patients)

	Surgeons A	B	C	D	E	F	G
Enflurane (*n* = 608)	61	84	82	141	159	60	21
Isoflurane (*n* = 570)	70	80	95	133	122	51	19

There were no significant differences between the groups (*P* = 0.42).

Table 3. Characteristics of Surgery

	Enflurane (*n* = 608)	Isoflurane (*n* = 570)	*P*
No. of CABG	3.3 ± 1.2	3.2 ± 1.1	0.29
Use of cardioplegia (%)	13.7	16.3	0.17
Cross-clamp time (min)	34 ± 14	35 ± 15	0.68
CPB time (min)	84 ± 27	86 ± 29	0.26
Operation time (min)	168 ± 38	173 ± 49	0.054

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass. Values are expressed as mean ± SD, except that for use of cardioplegia.

Table 4. Intraoperative Administration of Vasodilators

	Enflurane (*n* = 608)	Isoflurane (*n* = 570)	*P*
Nitroglycerin			
Before CPB	402 (66.1%)	312 (54.7%)	<0.001
After CPB	462 (76.0%)	403 (70.7%)	0.04
Nifedipine			
Before CPB	11 (1.8%)	13 (2.3%)	0.56
After CPB	14 (2.3%)	16 (2.8%)	0.58

CPB, cardiopulmonary bypass.

ysis, it was discovered that this weekly alternation schedule was not perfectly followed. *P* values less than 0.05 were considered to be statistically significant.

Results

As their primary anesthetic agent, 570 patients received isoflurane and 608 patients enflurane. Both groups were similar in risk factors (Montreal Heart Institute Risk Classification Index) and in other preoperative characteristics with the one exception of the incidence of a history of renal insufficiency, which was more frequent in patients given isoflurane (Table 1). There was also no significant difference between the groups in the assignment of the seven operating surgeons (Table 2) and in other surgical characteristics (Table 3). A difference was found, however, in the intraoperative administration of vasodilators. More patients in the enflurane group received nitroglycerin infusion in the pre- and postbypass periods (Table 4).

Among the 570 patients given isoflurane, 12 (2.1%) died (Table 5). Eleven deaths occurred as a direct result of heart failure or arrhythmia. Precipitating events included, in six of the 11 patients, severe hemodynamic aberrations that commenced in the operating room. In addition to the administration of catecholamines, four of the six required an intraaortic balloon pump to be able to leave the operating room. In another three of the 11 patients, severe hemodynamic aberrations started immediately after arrival in the ICU. In the remaining two of the 11 patients, heart failure commenced 6 and 9 h after arrival in the ICU. Seven of the above patients had evidence of MI and were included in the group considered to have MI. The 12th patient died of multisystem failure. The precipitating factor was considered to be low cardiac output.

Of the 608 patients who received enflurane, two (0.3%) died. In both patients, hemodynamic aberrations that started in the operating room were attributable to MI. The difference in mortality between the

Table 5. Incidence of Postoperative Myocardial Infarction, In-Hospital Mortality, and Difficult Weaning From Cardiopulmonary Bypass

	Enflurane (n = 608)	Isoflurane (n = 570)	P
MI (total)	11 (1.8%)	23 (4.0%)	0.023
Q waves	18 (3.0%)	32 (5.6%)	0.024
CK-MB>40	23 (3.8%)	32 (5.6%)	0.13
Deaths (total)	2 (0.3%)	12 (2.1%)	0.006[a]
Event in OR	2 (0.3%)	6 (1.1%)	
Event on arrival		3 (0.5%)	
Event 6 h after operation		1 (0.2%)	
Event 9 h after operation		1 (0.2%)	
Multisystem failure		1 (0.2%)	
MI (dead)	2 (0.3%)	7 (1.2%)	0.08
Difficult weaning			
Dopa/epineph	30 (4.9%)	46 (8.1%)	0.029
IABP in OR	0 (0.0%)	4 (0.7%)	0.054[a]
Additional CPB	6 (1.0%)	9 (1.6%)	0.36

MI, myocardial infarction; OR, operating room; dopa/epineph, administration of dopamine, or dopamine and epinephrine; IABP, intraaortic balloon pump; CPB, cardiopulmonary bypass.

[a] By Fisher's exact test.

isoflurane and enflurane groups was statistically significant ($P < 0.01$).

Among the patients who survived, 16 who received isoflurane and nine who received enflurane suffered MI. Thus, the incidence of MI was 4.0% (16 plus 7 patients) in the isoflurane group and 1.8% (9 plus 2 patients) in the enflurane group. The difference was statistically significant ($P < 0.05$). Because the definition of MI varies among institutions, data on CK-MB and Q waves are separately shown in Table 5. The difference in the number of new Q waves between the two groups was statistically significant, but the difference in positive CK-MB values was not significant.

Ease of termination of CPB was evaluated in terms of the frequency of catecholamine administration and in the requirement of additional CPB (for reperfusion or revision of grafts) and/or an intraaortic balloon pump. Forty-six patients (8.1%) in the isoflurane group and 30 patients (4.9%) in the enflurane group required catecholamine (dopamine alone or dopamine and epinephrine) in the operating room ($P < 0.05$). Of those who needed catecholamine, MI was diagnosed in 10 patients in the isoflurane group (six survived) and in four in the enflurane group (two survived). Additional CPB was required in nine patients in the isoflurane group and in six in the enflurane group (not a significant difference). As mentioned above, an intraaortic balloon pump was implanted in the operating room in four patients of the isoflurane group but in none of the enflurane group (not a significant difference).

As stated in Methods, the allocation of patients was not randomized, and therefore we looked for any difference in preoperative and surgical characteristics between the two groups, using uni- and multivariate analysis to determine if any factor in preoperative patient characteristics and assignment of surgeons could be a predictor of cardiac outcome. A history of renal insufficiency was the only factor, other than the anesthetic agent, that we could find to be different between the groups. However, the former did not influence outcome because none of patients with a history of renal insufficiency died and only one of them had postoperative MI. Thus, the anesthetic agent was the only factor that we could find to be related to the observed differences in cardiac outcome.

Discussion

Our results demonstrate that isoflurane negatively influences outcome after coronary artery surgery. Outcome depends, however, on many factors, including preoperative patient characteristics, anesthetic techniques, and—very important—surgical factors. The conclusion of our study is based on the assumption that any factors other than the choice of anesthetics did not differ between the groups. We believe that the preoperative risk factors that might have influenced outcome were randomized as the evaluation of the Montreal Heart Institute Risk Classification Index showed no difference between groups. Anesthetic management was not standardized in detail for the present study except for the choice of volatile anesthetics, but rather each anesthesiologist managed the patient at his or her own discretion. We considered this to be the norm in clinical practice, and, in such a large number of patients, differences in management should have been averaged out in both groups. Finally, surgical factors, including the technical quality of each operation, which should have played an essential role in determining outcome, were not evaluated in the present study. Therefore, we do not know to what extent technical problems in surgery contributed to the difference in outcome between the groups. We believe, however, that the similar assignment of each surgeon to both anesthetics and a large patient population eliminated inequality in surgical skill and judgment as a factor in determining differences in outcome between the two groups of patients in our study.

To our knowledge, two additional CABG outcome studies have been reported. Both showed, in contrast to our results, no deleterious effects of isoflurane in coronary artery surgery (11,12). In one study, volatile anesthetics were used as supplements to intravenous agents (12); in the other study, volatile agents were used as the primary anesthetic agent (11), as in our study. The major difference between the latter study (11) and ours seems to lie in management during CPB. In that study, volatile agents were not used in all cases as the primary anesthetic during CPB, whereas in our study they were used in all patients. In addition, different methods were used for myocardial protection during CABG. In the other study, after infusion of cardioplegic solution the aorta was cross-clamped for the whole time during distal vein graft anastomoses, whereas in most of our patients cardioplegic solutions were not used, i.e., coronary arteries were intermittently perfused with cold blood containing a volatile agent between successive anastomoses of distal vein grafts.

Intermittent aortic cross-clamping without cardioplegia was mostly used in the 1960s and early 1970s. The favorable factors of intermittent cross-clamping are that, first, it is easy to perform and, second, identifying the appropriate site for incision in a coronary artery may be easier with intermittent cross-clamping than with cardioplegia because coronary arteries are filled with blood using the former technique but with clear crystalloid solution using the latter. The cold cardioplegic technique appears, however, to be superior to the intermittent cross-clamping for myocardial protection (13,14). Thus, today most surgeons use cold cardioplegic myocardial protection. Some surgeons have, nonetheless, reported excellent clinical outcomes using the intermittent cross-clamping technique (15,16), and this method continues to be used in some clinics for CABG. Good results with this method are also evident in the overall MI rate (2.9%) and mortality (1.2%) in our study, in which 85% of CABGs were done without cardioplegia.

Until the start of CPB, there were some differences in anesthetic technique between our study and that of Slogoff and Keats (11), including, for example, the fact that they administered more fentanyl for induction of anesthesia than we did, but did not use nitrous oxide for maintenance of anesthesia. Because administered concentrations of volatile agents were not reported (11), we cannot infer different consequences derived from these differences in management. We think, however, that there might have been only minimal differences between both studies in the administration of volatile agents until the start of CPB because the reduction of MAC by the higher dose of fentanyl in their study (11) should have been offset by the fact that they did not use nitrous oxide. Thus, if differences in management between their study and ours occurred mainly during CPB, it is tempting to speculate that CPB was the period when deleterious effects of isoflurane on myocardium became manifest, i.e., the myocardium may have been damaged or not sufficiently protected during reperfusion periods more often with isoflurane.

We cannot, of course, conclude from the present study that, as the result of coronary steal, isoflurane led to higher incidence of difficult weaning from CPB, higher incidence of MI, and higher mortality. Causes other than coronary steal may have contributed to the detrimental effect of isoflurane on cardiac outcome.

Unfortunately, we did not prospectively study differences in hemodynamic parameters between both groups. The fact that nitroglycerin was more often administered in the enflurane group both in the pre- and post-CPB periods may suggest, however, that blood pressure tended to be higher in the enflurane group. Thus, there might have been differences in anesthetic management due to the different characters of these anesthetics. Nevertheless, because the purpose of our study was to investigate differences in outcome when enflurane and isoflurane were used as a clinical routine, we present our results as a cautionary note regarding the routine use of isoflurane in patients undergoing CABG, irrespective of the cause of the observed differences in outcome.

References

1. Reiz S, Balfors E, Sorensen MB, Ariola S Jr, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.
2. Moffitt EA, Barker RA, Glenn JJ, et al. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. Anesth Analg 1986;65:53–61.
3. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.
4. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 1988;67:936–42.
5. O'Young J, Mastrocostopoulos G, Hilgenberg A, Palacios I, Kyritsis A, Lappas DG. Myocardial circulatory and metabolic effects of isoflurane and sufentanil during coronary artery surgery. Anesthesiology 1987;66:653–8.
6. Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF. Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: their capacity to induce coronary steal. Anesthesiology 1987;67:665–75.

7. Tarnow J, Markschies-Hornung A, Schulte-Sasse U. Isoflurane improves the tolerance to pacing-induced myocardial ischemia. Anesthesiology 1986;64:147–56.

8. Paiment B, Pelletier C, Dyrda I, et al. A simple classification of the risk in cardiac surgery. Can Anaesth Soc J 1983;30:61–8.

9. Empfehlungen der Deutschen Gesellschaft für Klinische Chemie (DGKC). J Clin Chem Clin Biochem 1977;15:249–54.

10. Neumeier D, Prellwitz W, Würzburg U, et al. Determination of creatine kinase isoenzyme MB activity in serum using immunological inhibition of creatine kinase M subunit activity—activity kinetics and diagnostic significance in myocardial infarction. Clin Chim Acta 1976;73:445–51.

11. Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989;70:179–88.

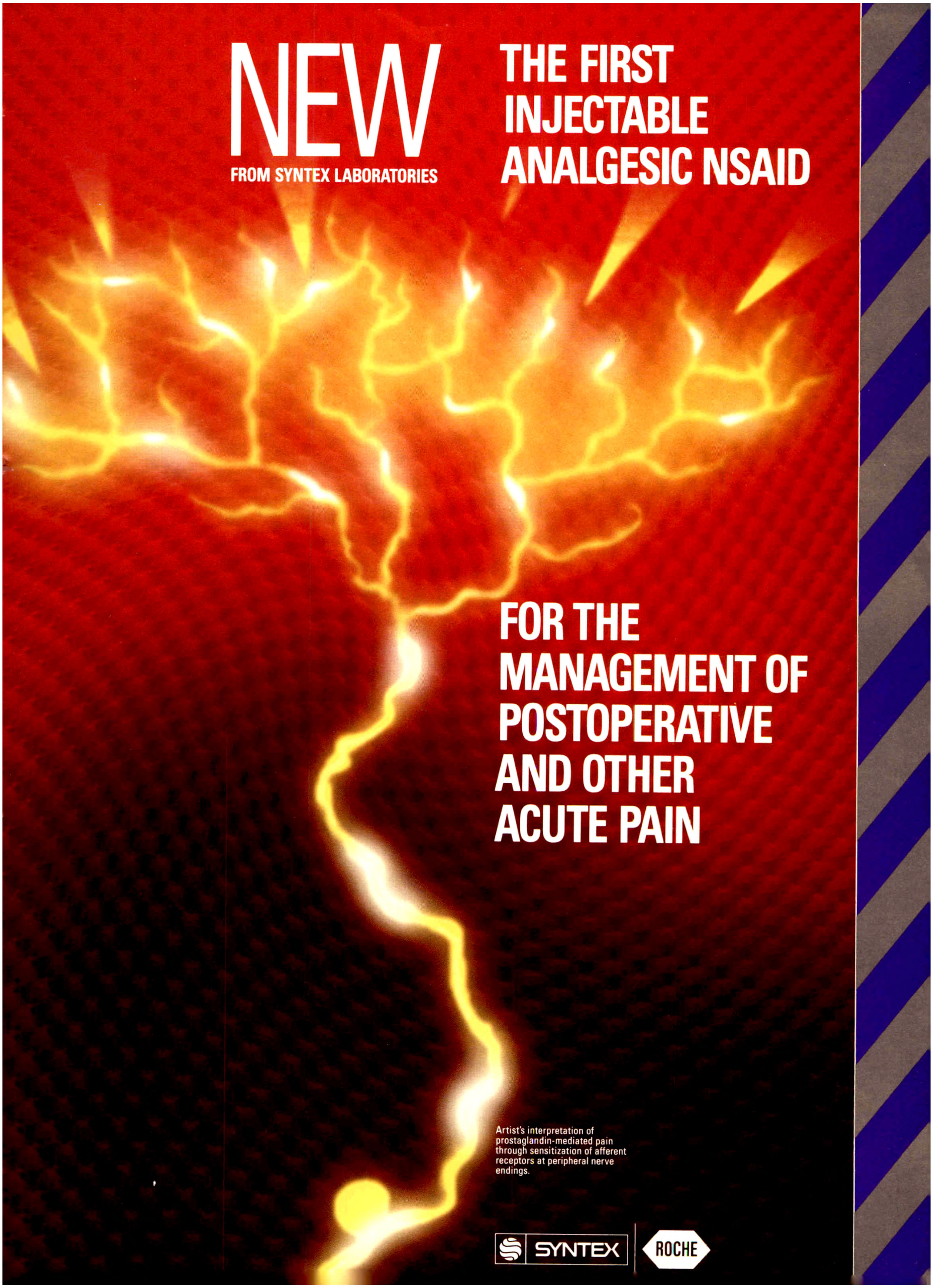
12. Tuman KJ, McCarthy RJ, Spiess BD, DaValle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 1989;70:189–98.

13. Laks HL, Barner HB, Standeven JW, Hahn JW, Jellinek M, Menz LJ. Myocardial protection by intermittent perfusion with cardioplegic solution versus intermittent coronary perfusion with cold blood. J Thorac Cardiovasc Surg 1978;76:158–72.

14. Alfieri O, Vermeulen FEE, Knaepen PJ, De Geest R, Huysmans HA, Schaepkens van Riempst ALEMS. Extensive myocardial revascularization—influence of cardioplegia on operative results. Thorac Cardiovasc Surg 1980;28:343–7.

15. Roberts AJ, Sanders JH Jr, Moran JM, et al. Nonrandomized matched pair analysis of intermittent ischemic arrest versus potassium crystalloid cardioplegia during myocardial revascularization. Ann Thorac Surg 1980;31:502–11.

16. Flameng W, van der Vusse GJ, Borgers M, de Meyere R, Suy R. Intermittent aortic crossclamping at 32°C, a safe technique for multiple aortocoronary bypass grafting. Thorac Cardiovasc Surg 1981;29:216–22.



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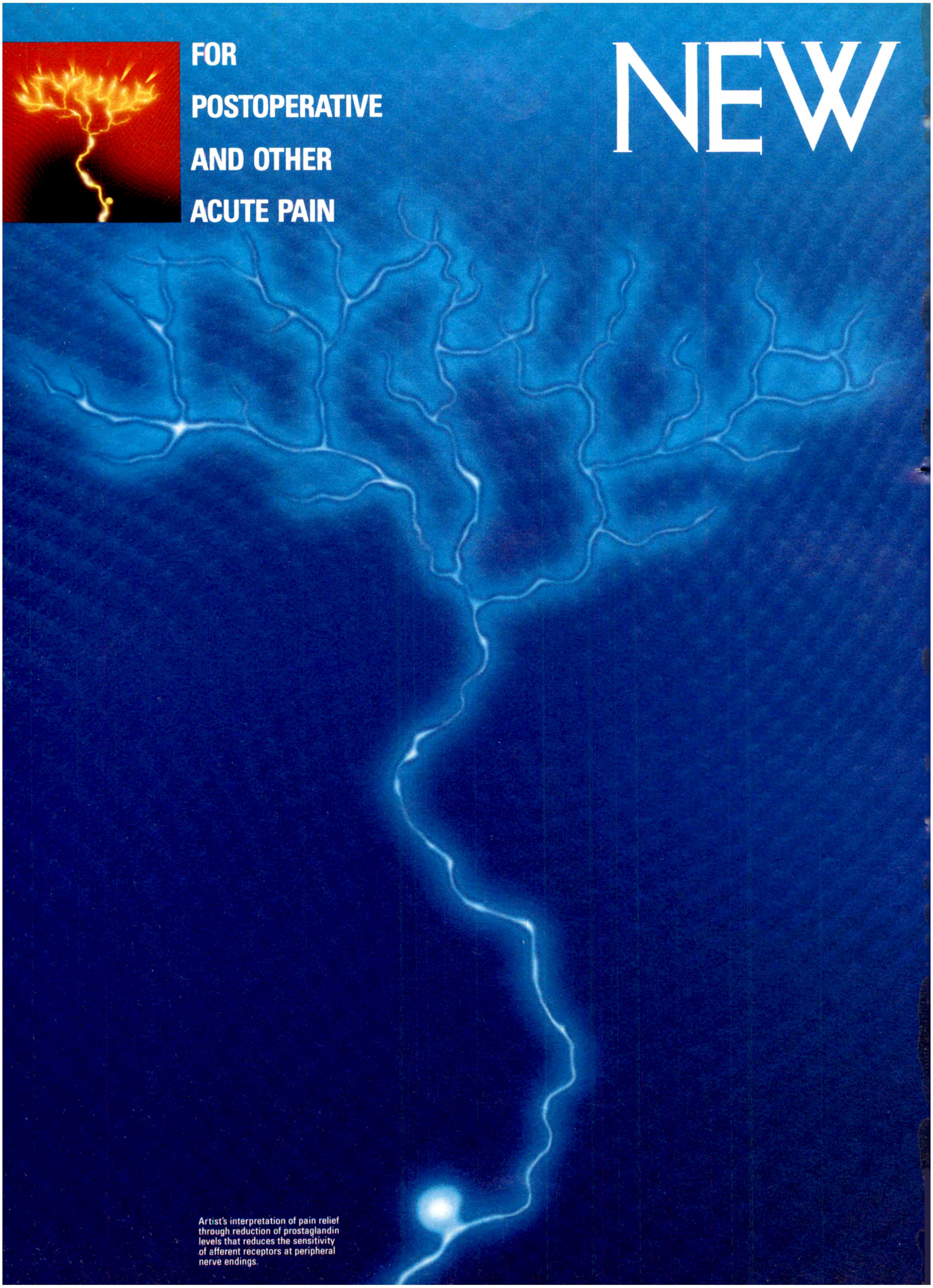

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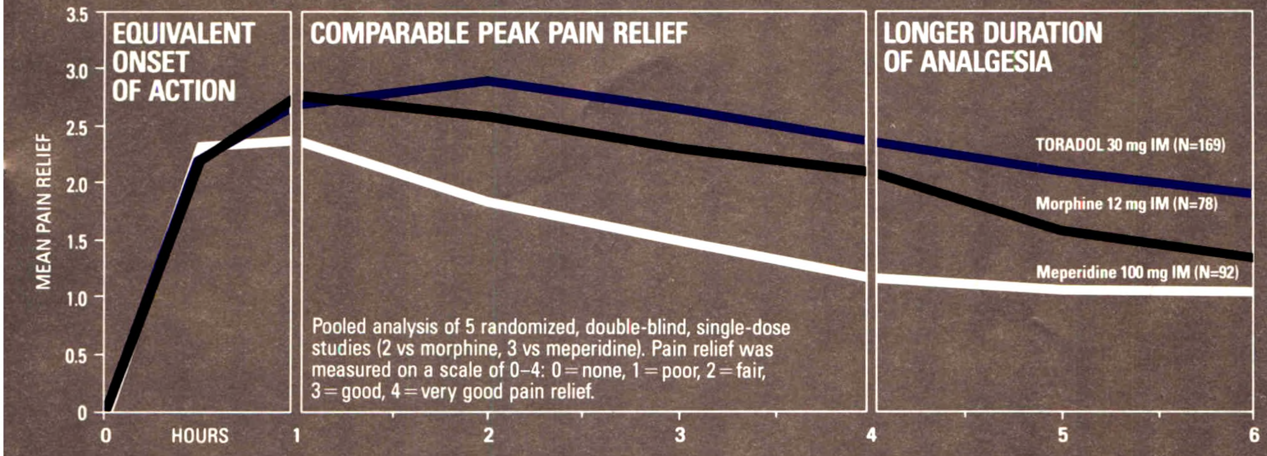
Analgesic efficacy of TORADOL IM administered 24–72 hours postsurgery[1]



Pooled analysis of 5 randomized, double-blind, single-dose studies (2 vs morphine, 3 vs meperidine). Pain relief was measured on a scale of 0–4: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = very good pain relief.

Documented efficacy following a broad range of surgical procedures:

General, orthopaedic, gynecologic (not for obstetric use)

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings" and "Precautions" sections of prescribing information.

[1] Data on file, Syntex Laboratories, Inc., Document #90037-1.

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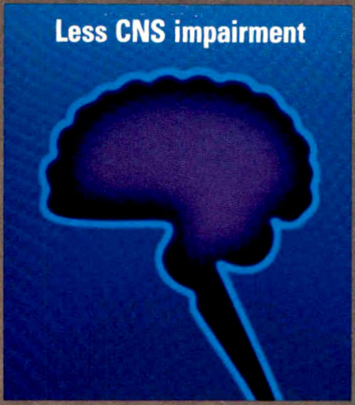

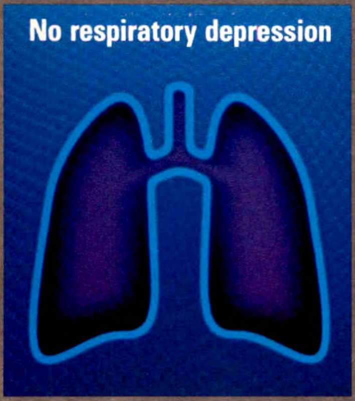

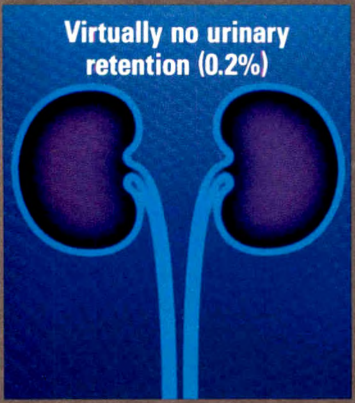

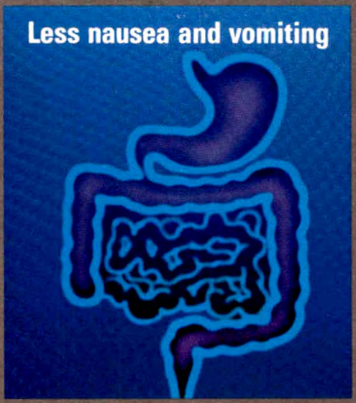

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- 62% less nausea and 44% less vomiting
- 48% fewer CNS side effects
- No respiratory depression
- No hypotension
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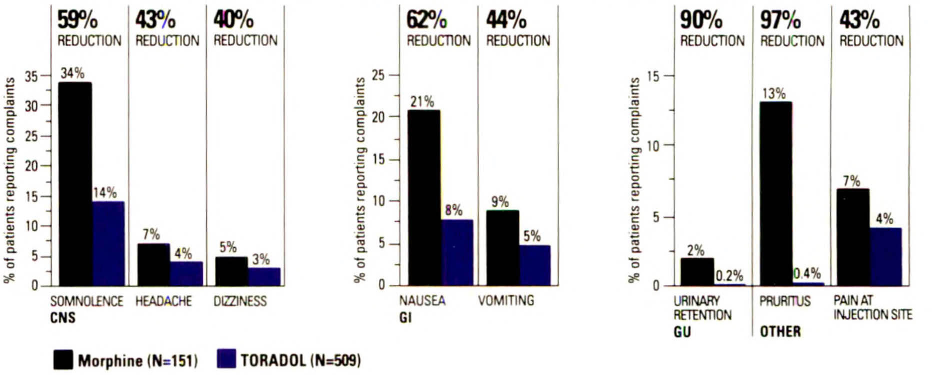
- No difference in clinically significant postoperative bleeding with TORADOL IM (0.4%) as compared to opiates (0.2%)

Comparison of most frequently reported side effects in 2 multi-dose studies (TORADOL IM vs morphine)**



Adverse reactions rates from short-term use of NSAIDs are generally from 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL IM.

FOR POSTOPERATIVE AND OTHER ACUTE PAIN

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

**Most frequently reported side effects in major body systems with the exception of the cardiovascular system. 2% of patients treated with Toradol reported vasodilation as compared to 1% of patients treated with morphine.

1. Documented in 2 randomized, double-blind, multi-dose studies in which 509 patients received ketorolac 30 mg and 151 patients received morphine 10 mg or morphine 12 mg. Bowel function was evaluated in a subset of 47 patients undergoing gastric bypass surgery. Data on file, Syntex Laboratories, Inc., Document #90037-2.
2. Data on file, Syntex Laboratories, Inc., Document #90037-3.

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Analgesic therapy well suited for postoperative use

TORADOL IM is not an opiate

- Does not act on opiate receptor sites
- No potential for abuse
- No special restrictions or controls required

May be an appropriate alternative to narcotics for:

- Patients with narcotic allergy or intolerance
- Patients with a history of, or potential for, drug abuse or dependence

Special advantages may facilitate postoperative recuperation

- Patients with COPD or the obese—no negative effects on pulmonary function
- Ambulatory surgery patients—less CNS impairment (e.g., 59% less somnolence and 40% less dizziness)

Optimize analgesia on the day of surgery

- On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing
- On average, only one supplemental dose of narcotics may be required[2]

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(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

FOR POSTOPERATIVE AND OTHER ACUTE PAIN

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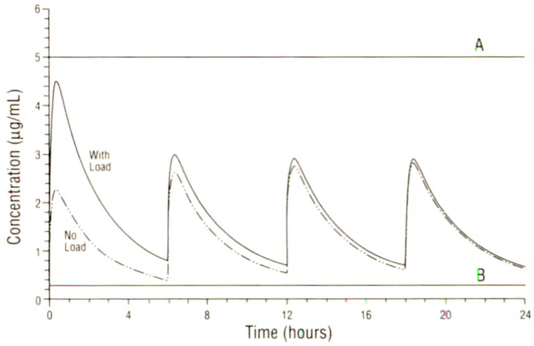
OPTIMIZE ANALGESIC THERAPY FOR THE POSTOPERATIVE PATIENT

PROPER DOSAGE POSTOPERATIVELY
For maximum analgesia:

- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*



Simulated incremental plasma concentrations after 2 multi-dose regimens: (1) TORADOL IM 30 mg Q6h (no load); (2) TORADOL IM 60 mg LOADING DOSE followed by 30 mg Q6h

A = Plasma concentration above which side effects are more frequent

B = Estimated concentration required to obtain 50% decreases in pain intensity scores in dental surgery pain

Achieve optimal peak and trough plasma levels by starting with a loading dose (e.g., 60 mg), while maintaining plasma levels within the recommended therapeutic range. Follow with maintenance doses (e.g., 30 mg every 6 hours) to keep plasma levels in the optimal range.

Patient Selection: Use in patients with moderate-to-severe postoperative pain following general, orthopaedic, or gynecologic surgery (not for obstetric use)

Lower doses:

- Recommended for patients under 50 kg (110 pounds), patients over 65 years of age, and patients with reduced renal function
- Start with loading dose of 30 mg IM
- Follow with maintenance dose of 15 mg IM Q6h to control pain

On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing (not compatible in same syringe)

*Dosages above those recommended are not associated with commensurate increases in efficacy.

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TORADOL® IM (ketorolac tromethamine)

Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

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(atracurium besylate)

References and brief summary of full prescribing information can be found on the following page.

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*Nondepolarizing neuromuscular blocking agents.

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Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of $\geq$ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses $\leq$ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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1. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology.* 1984;61:444-453.
2. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172.
3. Lawson DH, Paice GM, Glavin RJ, et al. Atracurium — a post-marketing surveillance study: U.K. study and discussion. *Br J Anaesth.* 1989;62:596-600.

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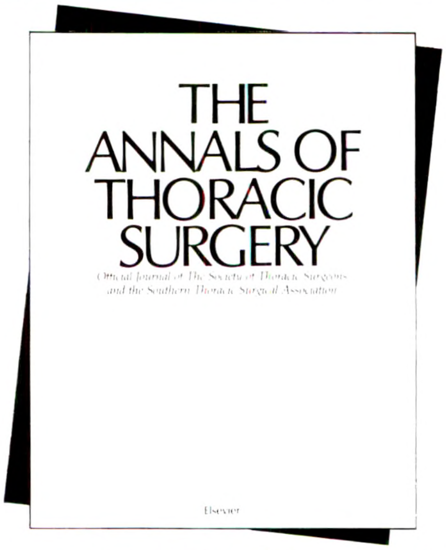
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1990 Subscription Information, Vol. 49, 50 (12 issues)
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For additional information contact: Edward Stullken, M.D., Chairman, Department of Anesthesiology, WVU Health Sciences Center, Morgantown, WV 26506. Telephone: (304) 293-5411.

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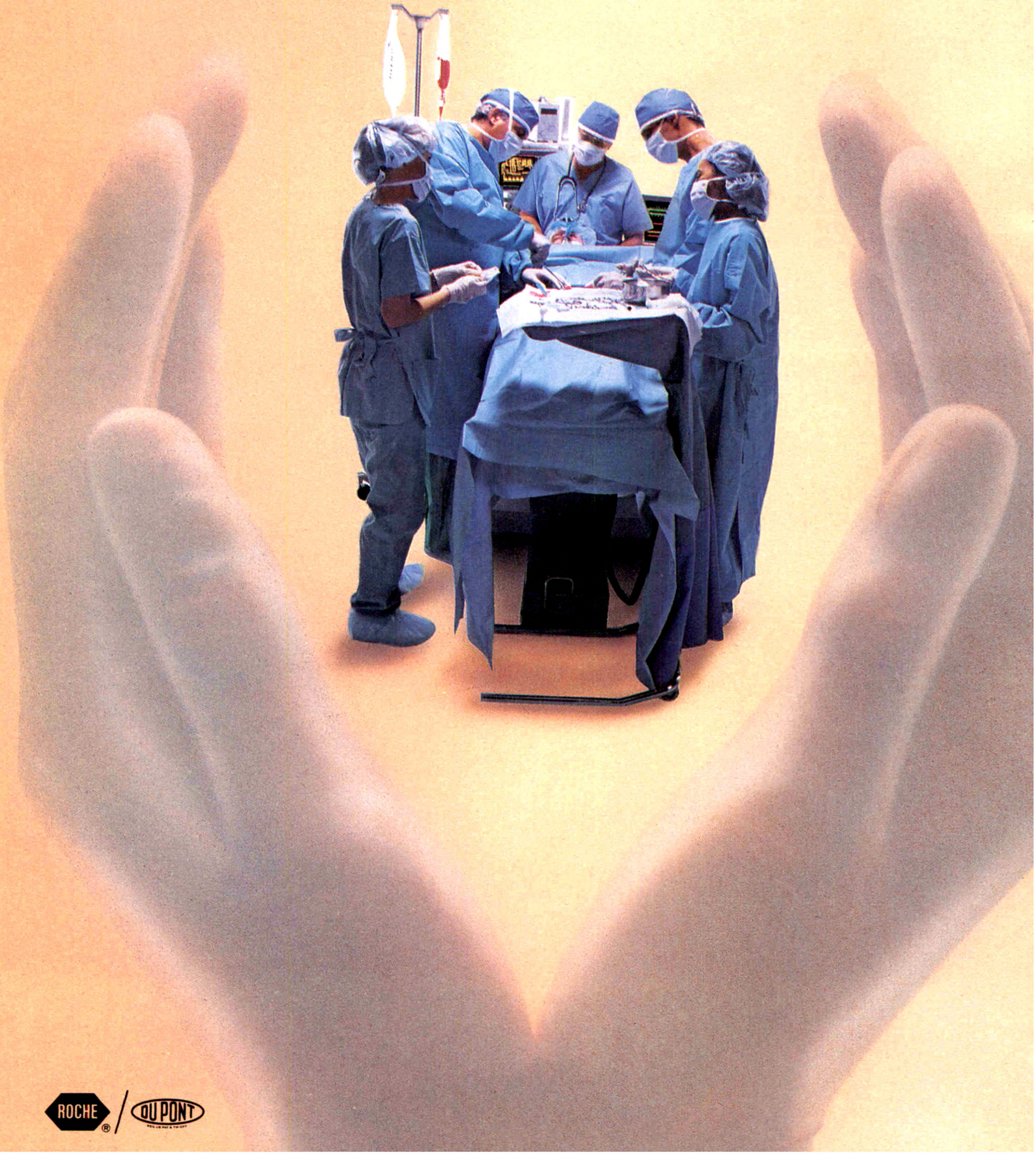

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References: 1. Roche Scientific Summary. The Evaluation of VERSED® (brand of midazolam HCl/Roche) Ⓒ, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, New Jersey, 1986. **2.** White PF. *Anesthesiology.* 1982;57:279-284. **3.** Data on file (Abs. #069-005), Hoffmann-La Roche Inc., Nutley, New Jersey.

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> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1mg/mL formulation or dilution of the 1mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.

Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses. Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

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Low-Dose Almitrine Bismesylate Enhances Hypoxic Pulmonary Vasoconstriction in Closed-Chest Dogs

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CHEN L, MILLER FL, CLARKE WR, CLERGUE FX, MARSHALL C, MARSHALL BE. Low-dose almitrine bismesylate enhances hypoxic pulmonary vasoconstriction in closed-chest dogs. Anesth Analg 1990;71:475–83.

The effect of almitrine bismesylate on the hypoxic pulmonary vasoconstrictor response was studied in six closed-chest dogs anesthetized with pentobarbital and paralyzed with pancuronium. The right lung was ventilated continuously with 100% O_2; the left lung was ventilated either with 100% O_2 ("hyperoxia") or with an hypoxic gas mixture ("hypoxia": end-tidal oxygen tension = 60.3 ± 0.6 mm Hg). On two consecutive days, each dog received either almitrine (Vectarion, Servier Lab) or malic acid. Consecutive almitrine doses of 0.003, 0.03, 0.3, and 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or the equivalent volumes of malic acid without almitrine, were administered intravenously as a constant peripheral infusion for 15 min. Percent blood flow to each lung was calculated based on a variation of the traditional shunt equation. The change in percent left lung blood flow ($\Delta\%\dot{Q}_{L\text{-}VA}$) increased significantly between the hypoxia-no drug and the hypoxia-almitrine (3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) phase. No significant changes occurred during the other almitrine doses or the respective malic acid control phases. The change in arterial oxygen tension (ΔPa_{O_2}) also increased significantly between the hypoxia-no drug and the hypoxia-almitrine (3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) phase. No significant changes occurred during the other almitrine doses or the respective malic acid control phases. It is concluded that in dogs low-dose almitrine enhances hypoxic pulmonary vasoconstriction and that this enhancement is dose-related.

Key Words: PHARMACOLOGY, ALMITRINE. RECEPTORS, CHEMO—almitrine. LUNG, OBSTRUCTIVE PULMONARY DISEASE—almitrine.

Almitrine bismesylate, a peripheral chemoreceptor agonist (1,2), improves arterial oxygen tension and reduces arterial carbon dioxide tension in patients with chronic respiratory failure associated with obstructive pulmonary disease. It has been proposed that this improvement in gas exchange is due to enhancement of hypoxic pulmonary vasoconstriction (HPV) (3,4). However, there is increasing evidence that the effects of almitrine are dose-dependent (5–7) because a low dose, it has been suggested, enhances the HPV response (8) whereas a moderate dose (9) has no effect on the HPV response and a high dose (10) inhibits the HPV response. The present study examined in closed-chest dogs this controversial dose-dependent effect with the hypothesis that low-dose almitrine enhances HPV.

Methods

Anesthesia and Surgery

Six female dogs of mixed breed with a mean weight of 19.9 ± 0.7 kg were anesthetized with a bolus of 30-mg/kg intravenous pentobarbital (Abbott Laboratories) followed by an infusion at 0.4–2.0 mg/min (Harvard Infusion Pump model 902). Because each dog was to be used as its own control on two consecutive days, direct laryngoscopy for tracheal intubation was performed rather than tracheostomy. With a Miller No. 3 blade, the trachea was intubated with a 39F bifurcated canine Kottmeier double-lumen endobronchial tube (Rüsch) using a Foerster 9.5-in curved sponge holding forcep with smooth jaws (Roboz Surgical Instrument Co.). Mechanical ventila-

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Supported in part by an ASA Starter Grant and by National Institute of General Medical Sciences grants GM29628 and GM07612.

Presented in part at the 1987 Meeting of the American Society of Anesthesiologists, Atlanta, Georgia.

Received from the Center for Research in Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Accepted for publication June 22, 1990.

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tion was begun. Muscle paralysis was established with 0.05-mg/kg intravenous pancuronium (Organon) supplemented by 0.2–0.5 mg every 30 min.

Complete lung isolation was verified by auscultation and demonstration that cross-contamination did not occur when the left lung was ventilated with an hypoxic gas mixture. A percent venous admixture of less than 8% during 100% oxygen (O_2) ventilation was used to confirm normal lung function and particularly that the right upper lobe bronchus was not obstructed by the double-lumen tube. The lungs were ventilated synchronously with 100% O_2 via a dual-piston respirator (Harvard Apparatus Respiration Pump model 618) with 5 cm H_2O of positive end-expiratory pressure applied by water seal. Tidal volumes were selected to produce equal peak airway pressures of 15–20 cm H_2O. Inspired carbon dioxide (CO_2) and/or the respiratory rate were adjusted to keep both the right and left end-tidal CO_2 tension (Pco_2) approximately equal and close to 35–40 mm Hg throughout the whole study. Each piston of the Harvard ventilator was part of a separate gas circuit, with its gas composition adjusted using separate flow meters for the right and left lung. Mixed expired gases were collected by passing the expired gas through a mixing unit (11). Right and left lung inspired, end-tidal, and mixed-expired O_2 tension (Po_2) and Pco_2 were measured by a mass spectrometer (Perkin-Elmer model 1100 Medical Gas Analyzer), which was calibrated daily with gases of known composition and corrected for barometric pressure, temperature, and water vapor.

Peripheral veins were cannulated for intravenous fluid administration to maintain euvolemia (278.9 ± 27.7 mL/h Normosol and/or 0.9% saline) and for infusion of almitrine. Body temperature, measured by an esophageal temperature probe, was maintained at 37.9 ± 0.3°C with heating lamps, pads, and heated humidifier. Sodium bicarbonate was available to correct metabolic acidosis. Urine was collected from a Foley catheter.

Based on observations from previous studies in our laboratory using a similar model, we observed that an infusion of 14.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine inhibited HPV (10), but that an infusion of 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine had no effect on HPV (9). Therefore, for the present study, a dose-response relationship was investigated. Consecutive almitrine doses of 0.003, 0.03, 0.3, 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or the equivalent volumes of malic acid without almitrine were administered via a constant peripheral intravenous infusion (Harvard Infusion Pump model 600-910/920).

Arterial pressure (via femoral artery) and central venous pressure (via an external jugular vein) were measured. Pulmonary arterial and pulmonary arterial occlusion pressures were measured with a flow-directed Swan–Ganz catheter (American Edwards 93A-131H-7F) placed percutaneously via a femoral vein. Pressures were measured continuously on an eight-channel Grass polygraph (model 7WC16PA). The zero pressure for the transducers (Statham model P23BB and Gould-Statham model P23Db) were set at midchest level. Thermodilution measurements of cardiac output (Edwards cardiac output computer model 9510-A) were made in triplicate using an injection of 5 mL of ice-cold 5% dextrose in water.

Blood flow to each lung was measured with a differential CO_2 elimination ($\dot{V}co_2$) method (10,12, 13). For each lung the expired gas was directed through a turbine spirometer with a digital electronic output (Boehringer Labs model 8830). Inspired, end-tidal, and mixed-expired CO_2 concentrations were measured using a mass spectrometer. Carbon dioxide production was calculated continuously from the expired volume signals and from the difference between the inspired and mixed-expired CO_2 concentration. The percent left lung blood flow ($\%\dot{Q}\text{L-}\dot{V}co_2$) was calculated as the CO_2 excretion from one lung divided by the total CO_2 excretion from both lungs, the quantity times 100. The calculation was as follows:

$$\%\dot{Q}\text{L-}\dot{V}\text{CO}_2 = \frac{(P\bar{E}\text{CO}_2\text{-L} - P\text{ICO}_2\text{-L})(V\text{T-L})}{(P\bar{E}\text{CO}_2\text{-L} - P\text{ICO}_2\text{-L})(V\text{T-L}) + (P\bar{E}\text{CO}_2\text{-R} - P\text{ICO}_2\text{-R})(V\text{T-R})} \times 100$$

with the mixed expired CO_2 tension for the left lung ($P\bar{E}CO_2\text{-L}$) and the right lung ($P\bar{E}CO_2\text{-R}$), and with the tidal volume for the left lung ($V\text{T-L}$) and right lung ($V\text{T-R}$). The excretion was corrected for the Haldane effect when one lung was ventilated with a hypoxic gas mixture (14).

Study Design

Before the experimental sequence, three 15-min trials of hypoxic (~4% O_2, 5% CO_2, balance nitrogen [N_2]) ventilation to the left lung were alternated with 100% O_2 ventilation to determine the presence of stable reproducible pulmonary blood flow and pressure responses to hypoxia (15).

On two consecutive days, each dog was randomized initially to receive either almitrine (Vectarion, Servier Lab) or malic acid. On each day the study was divided into six phases. The six phases were 100% O_2; hypoxia; and hypoxia with one of four doses of either almitrine or malic acid. Almitrine (15 mg) was dissolved in its solvent malic acid (5 mL) and then diluted with 0.9% saline solution (Abbott Laboratories). Consecutive almitrine doses of 0.003, 0.03, 0.3, and 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or the equivalent volumes of malic acid without almitrine were administered intravenously for 15 min. Measurements then required another 10–15 min for each phase.

The right lung was ventilated continuously with 100% O_2; the left lung was ventilated either with 100% O_2 (hyperoxia) or with an hypoxic gas mixture (hypoxia). With a flow meter (Matheson model 7481T, series R7400) to control inspired O_2, CO_2, and N_2, the left lung end-tidal Po_2 during hypoxia was maintained at 60.3 ± 0.6 mm Hg; this was chosen to yield an O_2 tension at the sensor site for HPV (Pso_2) that would produce a detectable but not maximal HPV response (16).

Measurements

At each phase, the following measurements were made: peak and mean airway pressure (P_{aw}), pulmonary artery pressure (PAP), systemic arterial pressure (SAP), central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), total cardiac output ($\dot{Q}_T$); body temperature; and inspired, end-tidal, and mixed expired O_2 and CO_2 concentration of each lung by mass spectrometer. Arterial and mixed venous blood samples were collected to determine pH, Po_2, Pco_2 (Corning pH/Blood Gas Analyzer model 168), and hemoglobin concentration (Sigma Kit No. 525). Right and left tidal volume (V_T), respiratory rate (RR), and minute ventilation ($\dot{V}_E$) were recorded.

Calculations

From the recorded data, blood flow, vascular resistance, and the percent blood flow to the left lung were calculated.

Pulmonary perfusion pressure (PPP) in mm Hg was calculated as mean PAP minus mean PAOP. Left and right pulmonary vascular resistances ($dyn \cdot cm^{-5} \cdot s$) were calculated from the perfusion pressure in mm Hg (× 80) divided by the respective lung blood flow in L/min.

Alveolar O_2 tension (P_{AO_2}) for the right lung ventilated with 100% O_2 was calculated from the barometric pressure minus the saturated water vapor pressure minus the arterial partial pressure of CO_2 ($Paco_2$). The left lung P_{AO_2} was estimated from the left lung end-tidal Po_2. End-capillary O_2 tension was assumed to be equal to the calculated alveolar O_2 tension. The O_2 contents (Co_2) of end-capillary, arterial, and mixed venous blood were then calculated from the following equation:

$$Co_2 = (1.34 \times Hb \times \%Sat) + (Po_2 \times 0.0031).$$

Percent saturation (%Sat), corrected for pH and temperature, was calculated from a nomogram for canine hemoglobin (Hb) (17).

Percent venous admixture (%VA) was calculated (18). Calculation of left lung blood flow was made by two methods. The first method, based on different CO_2 excretion of each lung, was described above as $\%\dot{Q}_L$-$\dot{V}co_2$. The second method for estimation of left lung blood flow during the hypoxic periods ($\%\dot{Q}_L$-VA) was based on a variation of the traditional shunt equation that allowed for the difference between alveolar O_2 tension of the hypoxic versus hyperoxic lung (19,20) (see Appendix). Two noninvasive methods for determining left lung blood flow were used as each of these methods has its own set of assumptions. The calculation for the hypoxic stimulus for HPV (Pso_2) is similar for the in vitro isolated perfused rat lung (18,21) and for in vivo dogs (22):

$$Pso_2 = (P\bar{v}o_2)^{0.38} \times (P_{AO_2})^{0.62},$$

where P_{AO_2} was assumed to be equal to the end-tidal O_2 tension (P_{ETO_2}).

Statistics

The data were analyzed by a one-way within-subjects analysis of variance (ANOVA) for repeated measurements with Neuman–Keuls test for specific differences. A value of $P < 0.05$ was considered statistically significant. Results are expressed as mean ± standard error.

Results

Because the general experimental conditions for pHa, $Paco_2$, temperature, hemoglobin, SAP, CVP, PAOP, mean airway pressure of the right lung (P_{awR}), mean airway pressure of the left lung (P_{awL}), tidal volume of the right lung ($V_{T\text{-}R}$), tidal volume of the left lung ($V_{T\text{-}L}$), minute ventilation of the right lung ($\dot{V}_{ER}$), and minute ventilation of the left lung ($\dot{V}_{EL}$) did not change significantly between the 12 phases of the study, only the baseline measurements made during the 100% O_2-no malic acid phase are presented in Table 1.

Table 1. General Hemodynamic and Blood Gas Values During the 100% O$_2$-No Malic Acid Condition (n = 6)

pHa	7.36 ± 0.012
Paco$_2$ (mm Hg)	38.9 ± 0.6
Temp (°C)	37.9 ± 0.3
Hb (g/dL)	12.2 ± 1.3
SAP (mm Hg)	135.5 ± 3.2
CVP (mm Hg)	3.3 ± 0.3
PAOP (mm Hg)	5.9 ± 0.8
P_{awR} (cm H_2O)	10.4 ± 0.2
P_{awL} (cm H_2O)	10.1 ± 0.1
VT-R (mL/min)	221 ± 13
VT-L (mL/min)	202 ± 12
$\dot{V}$ER (mL/min)	3260 ± 154
$\dot{V}$EL (mL/min)	2986 ± 165

pHa, arterial pH; Paco$_2$, arterial carbon dioxide tension; Temp, temperature; Hb, hemoglobin; SAP, mean systemic arterial pressure; CVP, mean central venous pressure; PAOP, mean pulmonary artery occlusion pressure; P_{awR}, mean airway pressure right lung; P_{awL}, mean airway pressure left lung; VT-R, mean tidal volume right lung; VT-L, mean tidal volume left lung; $\dot{V}$ER, minute ventilation right lung; and $\dot{V}$EL, minute ventilation left lung.

Values are mean ± SE.

The results with respect to the hypoxic pulmonary vasoconstrictor responses are listed in Table 2. Pao$_2$ decreased significantly between the 100% O$_2$ ventilation phase and the five hypoxic phases for both the almitrine and malic acid groups. The change in Pao$_2$ (ΔPao$_2$) between the hypoxia-no drug phase and the hypoxia-almitrine and/or malic acid phases was significantly different only for the hypoxia-3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase (Figure 1).

The percent left lung blood flow based on the traditional shunt equation (%$\dot{Q}$L-VA) decreased significantly between the hypoxia-no drug phase and the hypoxia-3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase (Figure 2). The change in percent left lung blood flow (%$\Delta\dot{Q}$L-VA) between the hypoxia-no drug and the hypoxia-almitrine and/or malic acid phases was significantly different only for the hypoxia-3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase (Figure 1).

The percent left lung blood flow based on differential CO$_2$ elimination technique (%$\dot{Q}$L-$\dot{V}$co$_2$) decreased significantly between the 100% O$_2$ ventilation and the hypoxia phases in both the almitrine and malic acid group. However, a further decrease occurred with administration of 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine, and this phase was significantly different from the other 11 phases.

The mean PAP increased significantly between 100% O$_2$ ventilation and the hypoxia phases in both the almitrine and the malic acid group. However, there was a further increase in PAP with the administration of 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine but not with malic acid infusion.

Mean pulmonary vascular resistances in the right lung (PVR_R) were never significantly different in either the almitrine or the malic acid group. The mean pulmonary vascular resistance for the left lung (PVR_L) increased significantly between hyperoxia and hypoxia. However, the PVR_L increased even further with the administration of the 3.0-$\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase, and this phase was significantly different from all other 11 phases.

$\dot{Q}$T increased significantly only between the first and sixth phase within the almitrine group, not in the malic acid group. There were no other significant differences between the two groups.

During the 3.0-$\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase, mixed venous oxygen tension (P$\bar{v}$o$_2$) increased significantly above the previous hypoxia-no almitrine phase and the hypoxia-0.003 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase.

During hypoxia, the end-tidal Po$_2$ in the left lung (PETO$_2$-L) and the stimulus for HPV (Pso$_2$) were not significantly different in either the almitrine or the malic acid group.

There was a tendency for heart rate to increase with time from the first to the sixth phases in both the almitrine group (148 ± 13 to 185 ± 12 beats/min) and the malic acid group (138 ± 15 to 185 ± 11 beats/min), but only in the malic acid group did this difference reach statistical significance.

Systemic vascular resistance was not significantly different between the 100% O$_2$-no almitrine and the hypoxia-no almitrine group (3950 ± 362 versus 3216 ± 188 $dyn \cdot cm^{-5} \cdot s$). However, systemic vascular resistance during the 100% O$_2$-no almitrine phase was significantly greater than it was in the four hypoxia-almitrine phases. There were no differences between the malic acid phases.

Discussion

This study examined a dose-response curve for the effect of almitrine on the right and left lungs during conditions of 100% O$_2$ ventilation and regional hypoxia. A low dose of almitrine was found to enhance hypoxic pulmonary vasoconstriction. The two major responses of HPV are a decrease in blood flow to the hypoxic lung and an increase in PAP, both of which occurred in this study. Indirect evidence supporting the conclusion that HPV was enhanced can be seen in the increases in Pao$_2$ and PVR_L.

Although $\dot{Q}$T during the hypoxia-3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase was increased above the 100% O$_2$-no drug phase, and although P$\bar{v}$o$_2$ increased above the hypoxia-no almitrine phase, these variables such as heart rate, may have represented a tendency to increase with time and perhaps with a change in

Table 2. Effects of Dose of Almitrine Bismesylate on Hemodynamic and Blood Gas Variables During Ventilation of the Left Lung With 100% O_2 or a Hypoxic Gas Mixture ($n = 6$)

	100% O_2	Hypoxia					100% O_2	Hypoxia				
			Almitrine infusion ($\mu g \cdot kg^{-1} \cdot min^{-1}$)						Malic acid infusion ($\mu L \cdot kg^{-1} \cdot min^{-1}$)			
	No alm	No alm	0.003	0.03	0.3	3.0	No malic acid	No malic acid	0.003	0.03	0.3	3.0
$\dot{Q}_T$ (L/min)	2.84	3.48	3.56	3.67	3.72	3.88	2.87	3.08	3.14	3.62	3.60	3.67
	±0.20	±0.10	±0.15	±0.19	±0.15	$\pm0.24^a$	±0.27	±0.31	±0.25	±0.22	±0.10	±0.22
Pa_{O_2} (mm Hg)	595	289	301	303	312	402	587	341	316	311	343	333
	±4	$\pm25^a$	$\pm22^a$	$\pm25^a$	$\pm30^a$	$\pm33^a$	±11	$\pm28^a$	$\pm35^a$	$\pm36^a$	$\pm34^a$	$\pm39^a$
$P\bar{v}_{O_2}$ (mm Hg)	60.6	53.9	56.2	58.7	61.1	65.4	61.6	54.6	56.3	58.5	58.2	59.3
	±3.6	±2.1	±1.6	±1.3	±1.4	$\pm1.4^b$	±3.3	±2.4	±2.3	±1.8	±2.0	±2.1
P_{ETO_2}-L (mm Hg)	674.0	60.3	60.2	60.2	60.3	60.0	672.0	60.2	60.0	59.8	60.3	59.8
	±1.5	$\pm0.6^a$	$\pm0.2^a$	$\pm0.3^a$	$\pm0.3^a$	$\pm0.4^a$	±3.9	$\pm0.3^a$	$\pm0.3^a$	$\pm0.2^a$	$\pm0.2^a$	$\pm0.2^a$
Ps_{O_2} (mm Hg)	57.9	58.6	59.6	60.6	61.8		57.9	58.5	59.3	59.5	59.6	
	±1.0	±0.7	±0.6	±0.7	±0.7		±0.9	±0.9	±0.7	±0.7	±0.8	
PAP (mm Hg)	16.0	19.9	20.7	21.1	22.1	22.6	14.9	18.0	19.6	19.7	20.0	20.6
	±1.2	$\pm1.6^a$	$\pm1.3^a$	$\pm1.1^a$	$\pm1.0^a$	$\pm1.2^{a,b}$	±1.0	$\pm1.1^a$	$\pm1.1^a$	$\pm0.7^a$	$\pm1.0^a$	$\pm0.9^a$
SVR ($dyn \cdot cm^{-5} \cdot s$)	3950	3216	3018	2990	2875	2730	3865	3667	3656	3062	3037	3033
	±362	±188	$\pm217^a$	$\pm282^a$	$\pm167^a$	$\pm233^a$	±372	±311	±351	±202	±42	±136
PVR_R ($dyn \cdot cm^{-5} \cdot s$)	559	492	501	479	511	444	472	462	488	432	450	448
	±91	±50	±55	±48	±53	±47	±65	±18	±33	±30	±22	±24
PVR_L ($dyn \cdot cm^{-5} \cdot s$)	674	1030	1135	1229	1398	2259	758	1121	1244	1150	1230	1257
	±67	±92	±139	±175	$\pm169^a$	$\pm387^{a,b,c}$	±174	±129	±148	±115	±144	±133
%VA	5.43						5.82					
	±0.70						±0.72					
$\%\dot{Q}_{L\text{-}VA}$		21.33	19.91	19.37	18.25	11.50		16.68	18.21	18.66	15.75	15.79
		±1.6	±1.93	±2.09	±2.78	$\pm2.01^b$		±1.10	±1.83	±1.99	±1.82	±1.86
$\%\dot{Q}_{L\text{-}\dot{V}CO_2}$	44.7	32.3	30.9	28.9	27.3	18.0	39.9	28.4	29.2	28.0	27.6	27.1
	±2.5	$\pm1.3^a$	$\pm2.3^a$	$\pm2.3^a$	$\pm2.7^a$	$\pm2.9^{a,b,c}$	±1.7	$\pm2.2^a$	$\pm2.8^a$	$\pm2.3^a$	$\pm2.4^a$	$\pm2.6^a$

[a] Significant difference from 100% O_2-no drug value ($P < 0.05$).
[b] Significant difference from hypoxia-no almitrine (alm) value ($P < 0.05$).
[c] Significant difference from all other values ($P < 0.05$).

the depth of anesthesia. These changes do not affect the interpretation of the results in that the stimulus for HPV (Ps_{O_2}), which is related to both P_{AO_2} and the $P\bar{v}_{O_2}$, was essentially the same in all 10 hypoxia phases (Table 1). Also, PAP increased while $\%\dot{Q}_{L\text{-}\dot{V}CO_2}$ decreased for an overall enhancement of HPV.

Almitrine infusion at 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was effective in increasing ΔPa_{O_2} compared with the hypoxia-no almitrine phases. The increase in $\dot{Q}_T$ resulted in an increase in $P\bar{v}_{O_2}$, thereby contributing to the improvement in Pa_{O_2}, but the reduction in $\%\dot{Q}_{L\text{-}VA}$ suggests that almitrine improved the ΔPa_{O_2} through a direct action on pulmonary gas exchange.

An increase in $\dot{Q}_T$ might be expected to increase PAP and to decrease PVR and HPV; however, in fact, the PVR did not decrease but increased significantly, suggesting that the increase in PAP was not due to the increased $\dot{Q}_T$ alone but to pulmonary vasoconstriction as well.

The solvent for almitrine, malic acid, has no effect on HPV (23,24). Also, malic acid is a normal constituent of blood (mean, 0.5 mg/100 mL; range, 0.1–0.9 mg/100 mL) (25,26). In the present study, malic acid again had no effect on the HPV response.

Redistribution of ventilation related to volume and pattern of breathing in the absence of significant changes in $\dot{V}_E$ has been suggested as a cause for the improved gas exchange with 100 mg oral almitrine in awake patients with chronic obstructive pulmonary disease (COPD) (27). In the anesthetized, paralyzed, mechanically ventilated animals used in this study, these types of changes are probably not a major contributing factor.

Another explanation for the observed ΔPa_{O_2} is an improved $\dot{V}_A/\dot{Q}$ matching attained through a redistribution of a portion of pulmonary blood flow. Using the multiple inert gas elimination technique, an improved $\dot{V}_A/\dot{Q}$ distribution has been observed in patients with COPD after 1.5 mg/kg oral almitrine (28) or 100 mg oral almitrine (3). Isotope studies before and after oral almitrine (either 1.5 or 3 mg/kg) in patients with COPD in the seated position (29) showed redistribution of blood flow from dependent lung regions to the better ventilated upper parts of

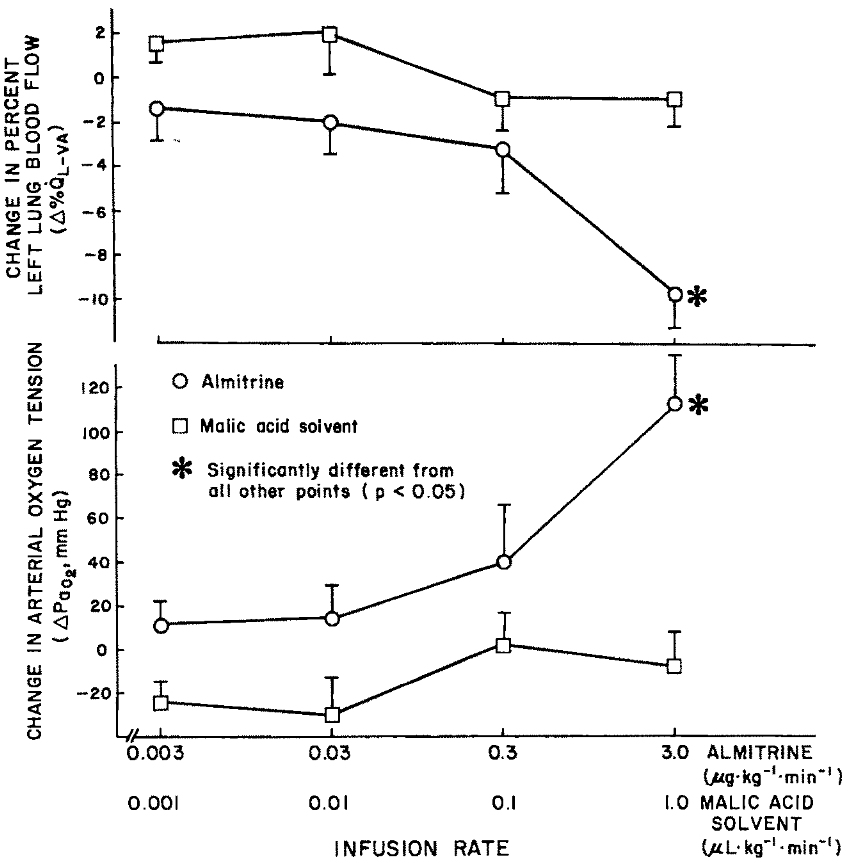

Figure 1. Relationship between the rate of infusion of almitrine or malic acid and both the change in percent left lung blood flow ($\Delta\%\dot{Q}$L-VA) and the change in arterial oxygen tension (ΔPao$_2$). The $\Delta\%\dot{Q}$L-VA and the ΔPao$_2$ between the hypoxia-no drug and the hypoxia almitrine and/or malic acid phase were significantly different for 3.0 μg·kg^{-1}·min^{-1} almitrine ($P < 0.05$). Almitrine (*open circle*); malic acid (*open square*).

the lungs with concomitant reduction of $\dot{V}$A/$\dot{Q}$ inequalities and improvement in blood gas tensions. In a double-blind randomized study in 16 patients with COPD (30), comparison of placebo versus oral almitrine (3 mg/kg) showed that almitrine significantly increased Pao$_2$, decreased Paco$_2$, and decreased the alveolar-arterial O$_2$ gradient without a significant change in ventilation; a ventilation lung scan and then a perfusion scan using krypton 81m showed a narrowing of the $\dot{V}$A/$\dot{Q}$ distribution with a decrease in both high and low $\dot{V}$A/$\dot{Q}$ zones; a significant but slight increase in mean PAP was also found.

The mechanism for the observed redistribution of pulmonary blood flow was initially attributed to enhancement of hypoxic pulmonary vasoconstriction by almitrine (4). Other animal evidence indicated that the pulmonary vasoconstriction induced by almitrine is present both in the hypoxic and hyperoxic areas (24). In humans, an increase in resting mean PAP has been reported by several different authors. Intravenous almitrine induced pulmonary vasoconstriction in both normal (31) and diseased (32) lungs. Macnee et al. (33), who administered 100 mg oral almitrine as one dose or 50 mg almitrine twice a day for a period of 3 mo, cautioned that this increase in PAP might worsen cor pulmonale in patients with COPD. In contrast, a double-blind placebo-controlled trial in patients with COPD showed no effect of oral almitrine (100 mg daily) on PAP over a 6-mo period (34); this has also been confirmed by others (28,35). Our previous results in dogs demonstrated that at sufficient dosage, almitrine may be a nonspecific pulmonary vasoconstrictor.

The results of the present study differ from two previous studies conducted in this laboratory using a slightly different study design. In the present study, smaller doses and shorter infusion durations were used; the four doses of almitrine and/or malic acid were infused for 15 min and then during the measurements, which required another 10–15 min for each phase. In the first study (9), the left lung end-tidal oxygen tension (Peto$_2$-L) during hypoxia was 29.0 ± 0.5 mm Hg, and a "moderate" dose of 3.3 μg·kg^{-1}·min^{-1} almitrine was infused for 30 min and then continuously while measurements were made for four phases, each of which required 30–40 min. This infusion rate was the same as that suggested by Romaldini et al. (4), who reported that almitrine enhanced HPV in a canine model of global hypoxia. In our study, almitrine, at a final plasma concentra-

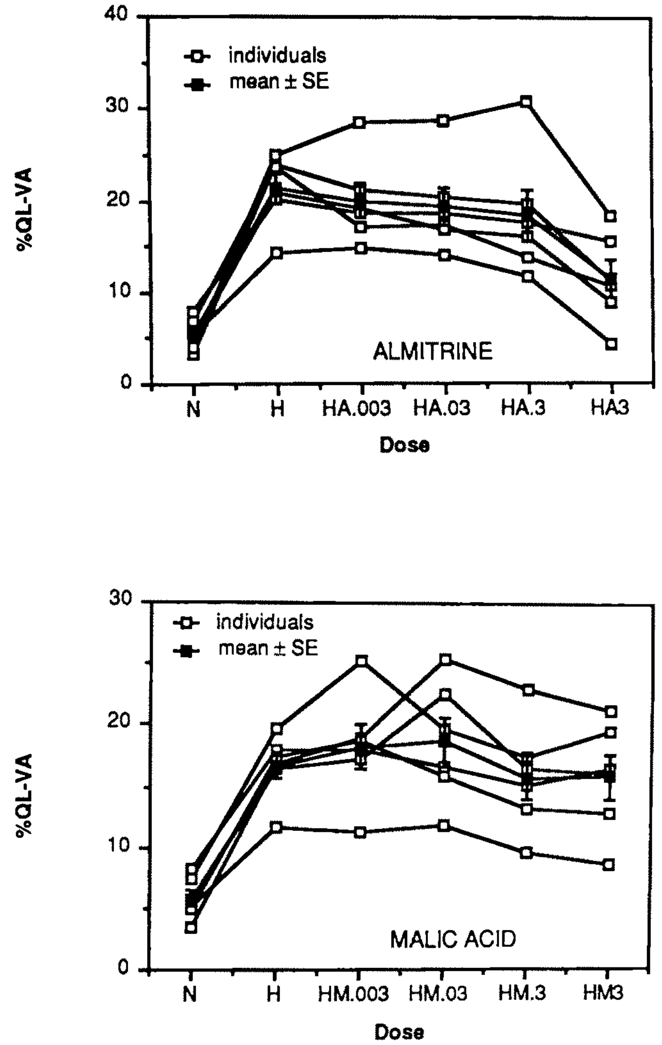

Figure 2. Relationship between dose of almitrine or malic acid and the percent left lung blood flow based on the traditional shunt equation (%$\dot{Q}$L-VA). The difference in %$\dot{Q}$L-VA values between the hypoxia-no drug and the hypoxia-almitrine or hypoxia-malic acid phases was significantly different only for the 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine phase ($P < 0.05$). Each individual animal (*open square*); mean ± SE (*filled square*); hyperoxia (N); hypoxia (H); almitrine infusion (A; $\mu g \cdot kg^{-1} \cdot min^{-1}$); malic acid infusion (M; $\mu L \cdot kg^{-1} \cdot min^{-1}$).

tion of 52.9 ± 4.4 ng/mL, had no effect on the HPV response. Consequently, a second study (10) was undertaken in which the study design was similar except that the almitrine infusion was increased to a "high" dose (14.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), which yielded a final plasma almitrine concentration of 219.5 ± 26.4 ng/mL. The PETO$_2$-L (50.1 ± 0.1 mm Hg) was increased to decrease the stimulus for HPV. This study showed that high-dose almitrine acted as a nonspecific pulmonary vasoconstrictor with its greatest effect on the vessels with the least initial tone.

Several animal studies as well as clinical studies have suggested that a revised dosage schedule may be required. Nakanishi et al. (8) studied open-chest beagles using electromagnetic flow probes to measure left lower lobe blood flow. The rest of the lung was ventilated with 100% O$_2$ and the left lower lobe with 95% N$_2$-5% CO$_2$. Then almitrine (0.3, 1, 3, and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused for 10 min before and for 10 min during hypoxia. Flow diversion increased significantly up to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before decreasing at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. From this study, Nakanishi et al. (8) suggest that HPV is enhanced by the low doses of almitrine and attenuated by the high dose of almitrine, which is consistent with the findings in our studies.

Reyes et al. (36) found that the intravenous infusion of 0.5 mg/kg almitrine in 30 min in patients with severe acute respiratory failure caused by sepsis or shock was accompanied by a substantial improvement in PaO$_2$ at 15 and 30 min, and a smaller but still significant improvement at 30, 60, 90, and 120 min after the end of the infusion. The authors suggested that different dosage schedules would be needed to attain longer lasting action of the drug on PaO$_2$.

Bell et al. (37) studied oral almitrine (100 or 50 mg twice a day) in 67 patients with COPD in a placebo-controlled double-blind study. PaO$_2$ increased significantly in both the 100- and 50-mg dose groups, but the increase was nearly twice as high in the high-dose group, suggesting a dose-related effect. PaCO$_2$ decreased significantly in the 100-mg group but not the 50-mg group. The major side effect was an unexplained worsening of dyspnea, which has been reported previously (38,39).

A possible explanation for this biphasic dose response is that in lung regions that are partially vasoconstricted, a low dose of almitrine increases the amount of vasoconstriction in these areas so that HPV is enhanced. As the dose of almitrine is increased, nonspecific vasoconstriction occurs in the nonhypoxic lung regions so that no effect on HPV is detected. When the almitrine dose is high, vasoconstriction of the hyperoxic lung regions occurs so that blood flow is diverted back into the hypoxic lung and HPV is diminished. This suggests that when used clinically, almitrine may be useful only in a very narrow dose range.

In summary, the present study shows that a properly low dose of almitrine can enhance hypoxic pulmonary vasoconstriction. Very low doses had no effect on the HPV response, but 15-min infusion at 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ resulted in specific vasoconstriction in the hypoxic lung and had no effect in the hyperoxic lung. From this study and others it has been determined that there is a biphasic dose-response curve where low doses enhance HPV, that moderate doses have no effect, and that very large doses inhibit HPV. Administration of almitrine to patients with COPD can be expected to improve oxygenation by enhancement of HPV in a very narrow dose range, a range that will have to be determined very carefully in each patient to define the proper dosage schedule for oral administration of almitrine.

The authors thank Johnathan Reed, BS, MS, for his technical assistance and Iris R. Karafin for preparation of the manuscript.

Appendix

Derivation of Hypoxic Shunt Equation (Reference 19)

Systemic arterial blood flow ($\dot{Q}_T$) consists of three components: mixed venous blood flow not perfusing ventilated alveoli within either lung ($\dot{Q}_S$), blood flow perfusing the hypoxic left lung ($\dot{Q}_H$), and blood flow perfusing the hyperoxic right lung ($\dot{Q}_T - \dot{Q}_S - \dot{Q}_H$).

Therefore, by mass balance, the total (bound and dissolved) O_2 in the blood flow through the lung is

$$\dot{Q}_T \times CaO_2 = \dot{Q}_H \times CHO_2 + \dot{Q}_S \times C\bar{v}O_2 + (\dot{Q}_T - \dot{Q}_S - \dot{Q}_H) \times Cc'O_2, \quad (1)$$

and, rearranging,

$$\dot{Q}_H/\dot{Q}_T = [(Cc'O_2 - CaO_2) - (\dot{Q}_S/\dot{Q}_T)(Cc'O_2 - C\bar{v}O_2)]/(Cc'O_2 - CHO_2). \quad (2)$$

Assuming that the anatomic shunt flow ($\dot{Q}_S/\dot{Q}_T$) measured during hyperoxia remains constant during corresponding hypoxic phases, then this equation is solvable. The final calculated admixture is

$$VA = \dot{Q}_H/\dot{Q}_T + \dot{Q}_S/\dot{Q}_T, \quad (3)$$

where an estimate of left lung blood flow is $\dot{Q}_H/\dot{Q}_T$, which multiplied by 100 is also designated ($\%\dot{Q}_{L\text{-}VA}$); this approximation consists of only the blood flow to ventilated lung regions.

These equations assume: (a) that the total anatomic shunt flow ($\dot{Q}_S/\dot{Q}_T$) measured during 100% O_2 ventilation remains unchanged during hypoxic ventilation for corresponding experimental conditions; and (b) that the apportionment of anatomic shunt flow whether to the right lung or the left lung also remains unchanged during hypoxic ventilation. The errors associated with these assumptions regarding the anatomic shunt flow during 100% O_2 ventilation were small compared to the variations in left lung flow during the experimental conditions.

References

1. Laubie M, Diot F. Etude pharmacologique de l'action stimulante respiratoire de S-2620. Role des chemorecepteurs carotidiens et aortiques. J Pharmacol 1972;3:363–74.
2. Laubie M, Schmitt H. Long-lasting hyperventilation induced by almitrine: evidence for specific effect on carotid and thoracic chemoreceptors. Eur J Pharmacol 1980;61:125–36.
3. Melot C, Naeije R, Rothchild T, Mertens B, Mols P, Hallimans R. Improvement in ventilation-perfusion matching by almitrine in COPD. Chest 1983;83:528–33.
4. Romaldini H, Rodriguez-Roisin R, Wagner PD, West JB. Enhancement of hypoxic pulmonary vasoconstriction by almitrine in the dog. Am Rev Respir Dis 1983;128:288–93.
5. Howard P, Voisin C, Ansquer JC. Long term trial of almitrine bismesylate in chronic obstructive airways disease. Vectarion International Multicentre Study Group (VIMS) (abstract). Am Rev Respir Dis 1987;135:A277.
6. Watanabe S, Cutillo AG, Kanner RE, Bachand RT. Long term effect of almitrine in hypoxemic COPD patients. One year trial (abstract). Am Rev Respir Dis 1987;135:A277.
7. Ryerson GG, Gotz V, Block AJ. Long term administration of almitrine bismesylate in chronic obstructive pulmonary disease (COPD) (abstract). Am Rev Respir Dis 1987;135:A278.
8. Nakanishi S, Hiramoto T, Ahmed MN, Nishimoto Y. Almitrine enhances in low dose the reactivity of pulmonary vessels to hypoxia. Respir Physiol 1988;74:139–50.
9. Chen L, Miller FL, Malmkvist G, Clergue F, Marshall BE. The effect of almitrine on hypoxic pulmonary vasoconstriction in dogs subjected to thoracotomy (abstract). Anesthesiology 1985; 63:A534.
10. Chen L, Miller FL, Malmkvist G, Clergue F, Marshall C, Marshall BE. High-dose almitrine inhibits hypoxic pulmonary vasoconstriction in closed-chest dogs. Anesthesiology 1987;67: 534–42.
11. Smith TC. Rapid continuous measurement of mixed expired carbon dioxide concentration. Anesthesiology 1968;29:1037–9.
12. Defares JG, Lundin G, Arborelius M, Stromland R, Svanberg L. Effect of unilateral hypoxia on pulmonary blood flow in normal subjects. J Appl Physiol 1960;15:169–74.
13. Chen L, Miller FL, Williams JJ, et al. Hypoxic pulmonary vasoconstriction is not potentiated by repeated intermittent hypoxia in closed chest dogs. Anesthesiology 1985;63:608–10.
14. Chen L, Miller FL, Aukburg SJ, Sedrak W, Marshall BE. Influence of the Haldane effect on measurement of intermittent hypoxic pulmonary vasoconstriction by intermittent hypoxia in dogs. Anesthesiology 1984;61:A480.
15. Pirlo AF, Benumof JL, Trousdale FR. Potentiation of lobar hypoxic pulmonary vasoconstriction by intermittent hypoxia in dogs. Anesthesiology 1981;55:226–30.
16. Marshall C, Marshall BE. Site and sensitivity for stimulation of hypoxic pulmonary vasoconstriction. J Appl Physiol 1983;55: 711–6.
17. Rossing RG, Cain SM. A nomogram relating Po_2, pH, temperatures, and hemoglobin saturation in the dog. J Appl Physiol 1966;21:195–201.
18. Berggren S. The oxygen deficit of arterial blood caused by non-ventilating parts of the lung. Acta Physiol Scand 1942;11: 1–92.
19. Glasser SA, Domino KB, Lindgren L, Parcella P, Marshall C, Marshall BE. Pulmonary blood pressure and flow during atelectasis. Anesthesiology 1983;58:225–31.
20. Domino KB, Chen L, Alexander CM, Williams JJ, Marshall C, Marshall BE. Time course and responses of sustained hypoxic pulmonary vasoconstriction in the dog. Anesthesiology 1984; 60:562–6
21. Marshall BE, Marshall C. Anesthesia and the pulmonary circulation. In: Covino BG, Fozzard HA, Rehder K, Strichartz G, eds. Effects of anesthesia. Baltimore: American Physiological Society, 1985:121–36.
22. Clarke WC, Pigott T, Costarino AT, et al. Combined effects of matched alveolar and pulmonary arterial oxygen tension on the pulmonary vascular resistance (abstract). Am Rev Respir Dis 1988;137:109.
23. Barer GR, Bee D, Wach RA, et al. Does almitrine bismesylate improve $\dot{V}/\dot{Q}$ matching? An animal study. Eur J Respir Dis 1983;64:209–14.

24. Hughes JMB, Allison DJ, Goatcher A, Tripathi A. Influence of alveolar hypoxia on pulmonary vasomotor responses to almitrine in the dog. Clin Sci 1986;70:555–64.
25. Hummel JP. The fluorometric determination of malic acid. J Biol Chem 1949;180:1225–8.
26. Altman P. Blood and other body-fluids. Washington, D.C.: Federation of American Societies for Experimental Biology, 1961:87.
27. Stradling JR, Nicholl CG, Cover D, Davies EE, Hughes JMB, Pride NB. Pattern of breathing and gas exchange following oral almitrine bismesylate in patients with chronic obstructive pulmonary disease. Eur J Respir Dis 1983;64:255–64.
28. Castaing Y, Manier G, Varene N, Guenard H. Effects de l'almitrine orale sur la distribution continue des rapport $\dot{V}_A/\dot{Q}$ dans les bronchopneumopathies chroniques obstructives. Bull Eur Physiopathol Respir 1981;17:917–32.
29. Rigaud D, Dubois F, Ansquer JC, Brambilla C, Godart T, Paramelle B. Modifications des rapports ventilation-perfusion dans les bronchopneumopathies chroniques obstructives apres administration de bismesilate d'almitrine. Bull Eur Physiopathol Respir 1982;18:339–50.
30. Simmoneau G, Meignan M, Denjean A, Rattestin B, Harf A, Prost JF. Cardiopulmonary effects of a simple oral dose of almitrine at rest and on exercise in patients with hypoxic chronic airflow obstruction. Chest 1986;89:174–9.
31. Gluskowski J, Gorecka D, Hawrylkiewicz I, Zielinski J. Acute effects of almitrine infusion on pulmonary hemodynamics in normal man. Bull Eur Physiolpathol Respir 1984;20:313–7.
32. Dull WL, Polu JM, Sadoul P. The pulmonary hemodynamic effects of almitrine infusion in men with chronic hypercapnia. Clin Sci 1983;64:25–31.
33. Macnee W, Connaughton JJ, Rhind GB, et al. A comparison of the effects of almitrine or oxygen breathing on pulmonary arterial pressure and right ventricular ejection fraction in hypoxic chronic bronchitis and emphysema. Am Rev Respir Dis 1986;134:559–65.
34. Paramelle B, Levy P, Pirotte C. Long term follow-up pulmonary arterial pressure evolution in COPD patients treated by almitrine bismesylate. Eur J Respir Dis 1983;64:333–6.
35. Melot C, Naeije R, Hallemans R, Mols P, Lejeune P. Beneficial effects of almitrine bisemesylate on pulmonary gas exchange in COPD. Eur J Respir Dis 1983;64:363–75.
36. Reyes A, Lopez-Messa TB. Alonso P. Almitrine in acute respiratory failure. Effects on pulmonary gas exchange and circulation. Chest 1987;91:388–93.
37. Bell RC, Mullins RC III, West LG, Bachand RT, Johanson WG Jr. The effect of almitrine bismesylate on hypoxemia in chronic obstructive pulmonary disease. Ann Intern Med 1986;105:342–6.
38. Naeije R, Melot C, Mols P, Hallemans R, Naeije N, Cornil A. Effects of almitrine in decompensated chronic respiratory insufficiency. Bull Eur Physiopathol Respir 1981;17:153–61.
39. Weitzenblum E, Ehrhart M, Schneider JC, Hirth C, Roegel E. Effects of intravenous almitrine on pulmonary hemodynamics in chronic bronchitis with respiratory insufficiency. Bull Eur Physiopathol Respir 1982;18:765–74.

Contributions of Liver Perfusion Flow Rate and Enzyme Inhibition to Altered Verapamil Clearance With Halothane: A Study in the Isolated Perfused Rat Liver

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FRINK EJ Jr, KRAMER TH, BANCHY SM, BROWN BR. Contributions of liver perfusion flow rate and enzyme inhibition to altered verapamil clearance with halothane: a study in the isolated perfused rat liver. Anesth Analg 1990;71:484–8.

Verapamil clearance is reduced during halothane administration. This study evaluated relative contributions of reduced hepatic flow rate and hepatic metabolizing enzyme inhibition by halothane as a cause of reduced verapamil clearance. An isolated perfused rat liver model was utilized in which flow rate could be fixed during halothane administration. Perfusions were performed on five to six livers under each of the following conditions: (a) control—40 mL/min flow rate with no anesthetic exposure; (b) 1.5% halothane—40 mL/min; (c) 2.25% halothane—40 mL/min; (d) reduced flow—20 mL/min with no anesthetic exposure; and (e) reduced flow with 1.5% halothane—20 mL/min.

Halothane caused dose-dependent decreases in both total hepatic and intrinsic clearance rates ($P < 0.05$). With no anesthetic exposure, a flow reduction of 50% (20 mL/min) also gave a large reduction ($P < 0.05$) in hepatic clearance of verapamil compared with the control condition (40 mL/min). The addition of 1.5% halothane to the reduced flow condition was not associated with further reduction in hepatic clearance rate. Results of this study suggest that although both reduced hepatic perfusion and hepatic enzymatic inhibition by halothane administration are associated with decreased verapamil clearance, a greater proportion of this decrease appears to be due to reductions in hepatic flow. The present results may apply to other drugs used in anesthesia that have high hepatic extraction ratios; thus, clearance of these drugs may be more dependent on hepatic blood flow than on hepatic enzyme activity.

Key Words: ANESTHESIA, VOLATILE—halothane. LIVER, BLOOD FLOW. PHARMACOLOGY, CALCIUM CHANNEL BLOCKER—verapamil. PHARMACOKINETICS, VERAPAMIL.

The hepatic clearance of parenterally administered drugs during the perianesthetic period can be altered by administration of inhalation anesthetics (1–3). Halothane and isoflurane, for example, decrease hepatic intrinsic clearance of propranolol in animals (1,2). In a study evaluating the interactions between verapamil and inhalation anesthetics, it was found that the administration of halothane, enflurane, or isoflurane increases steady-state plasma concentrations of verapamil with the greatest increases occurring during halothane exposure (3,4). In a subsequent study the effects of inhaled anesthetics on verapamil clearance were evaluated (5). The authors found that decreased intercompartmental clearance and, to a lesser extent, increased initial volume of distribution were associated with decreased verapamil clearance. Inhaled anesthetics are capable of decreasing total hepatic blood flow (6,7) as well as inhibiting hepatic oxidative biotransformation (8). Verapamil is a drug possessing a high hepatic extraction ratio and thus may exhibit hepatic clearance that is more dependent on hepatic flow than on hepatic enzyme activity. Recent work using an isolated perfused liver model has shown that the clearance of lidocaine and propranolol (both of which have high hepatic extractions) is decreased to varying degrees depending on the inhalation anesthetic administered (9). To evaluate the possible differential contributions of each of these variables (hepatic flow and hepatic enzyme inhibition) to altered verapamil clearance, we evalu-

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Received from the Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, Arizona. Accepted for publication July 9, 1990.

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ated verapamil clearance utilizing an isolated perfused rat liver system that allows for maintenance of constant hepatic flow rates during anesthetic exposure.

Methods

Twenty-eight male Sprague–Dawley rats (200–225 g, Harlan) were fed a standard diet and housed in hanging cages. After receiving institutional animal care committee approval, animals were anesthetized with intraperitoneal pentobarbital (65 mg/kg), with the portal vein cannulated using a 15-gauge blunt needle and perfused continuously during liver excision to remove blood and barbiturate. Liver perfusion during excision was at a rate of 30 mL/min (Cole Parmer pump) using Krebs–Henseleit buffer equilibrated with 95% oxygen (O_2)/5% carbon dioxide (CO_2). Excised livers were then immediately transferred to a glass isolated liver perfusion apparatus and perfused via the portal vein for study. All perfusions were performed utilizing a recirculating system with Krebs–Henseleit buffer as perfusate, equilibrated with 95% O_2/5% CO_2, pH 7.4 at 37°C. The perfusion apparatus used is constructed of glass parts (to prevent anesthetic absorption) and consists of a reservoir chamber, perfusate pumps, anesthetic equilibration chamber, and flow-rate regulating valve. Perfusate is passed through a rate-regulating valve to the liver via the portal vein and drains from the hepatic veins into a perfusate reservoir chamber. Perfusate is then returned above the liver via a continuous pump (Cole Parmer). The perfusate is equilibrated with O_2 and CO_2, with or without anesthetic agent as required, using a glass bead interface system before a return passage via the flow-rate regulatory valve through the liver. In this way, an ex situ reperfusion system is maintained with ability to alter perfusate anesthetic concentrations and flow rate.

Studies were made of five conditions: (a) control perfusions using perfusate equilibrated in the absence of halothane with 95% O_2/5% CO_2 at a flow rate of 40 mL/min; (b) reduced flow perfusions equilibrated with 95% O_2/5% CO_2 in the absence of halothane using a flow rate of 20 mL/min; (c) 1.5% halothane in 95% O_2/5% CO_2 at a flow rate of 40 mL/min; (d) 2.25% halothane in 95% O_2/5% CO_2 with flow rate of 40 mL/min; and (e) reduced flow (20 mL/min) plus 1.5% halothane in 95% O_2/5% CO_2. Verapamil (3.0 mg) was added to the 100-mL perfusate reservoir at the beginning of each perfusion for each of the study conditions (initial concentration in perfusate, 30 μg/mL). In all cases a 30-min perfusion was performed during which perfusate samples were obtained from the reservoir via a sampling port. Perfusate samples (250 μL) were removed from the reservoir via the sampling port at 1.5-min intervals throughout the perfusion and stored at −70°C for subsequent analysis. A total of five to six livers were perfused under each of the study conditions.

Perfusate samples were analyzed for verapamil concentrations using high-pressure liquid chromatographic analysis and (970 Schoeffel) fluorimetric detection (10). The daily variation for this assay was 5.1%.

The rate constants for verapamil elimination (−2.303 times the slope of the log concentration versus time plot) were determined by linear regression. The area under the concentration time curves (AUC) was obtained using the linear trapezoidal rule. Hepatic clearance (Cl_h), hepatic intrinsic clearance (Cl_i), and hepatic extraction ratio (E) were calculated as described below:

$$Cl_h = \frac{\text{Dose}}{\text{AUC}}, \tag{1}$$

$$E = \frac{Cl_h}{Q_h}, \tag{2}$$

$$Cl_i = \frac{Q_h \times E}{1 - E}, \tag{3}$$

where Q_h is the hepatic flow.

Specimens for histologic examination (hematoxylin and eosin stain) were obtained from all livers after perfusions to evaluate each for histologic evidence of hypoxia (swollen mitochondria and cytoplasmic vacuolization) (11). Statistical analysis of data utilized one-way analysis of variance with a post hoc Student–Newman–Keuls procedure to compare pharmacokinetic variables between groups. Statistical significance was defined as $P < 0.05$.

Results

Data from three liver perfusions were excluded based on histologic examination that showed cytoplasmic vacuolization suggestive of hepatocyte hypoxia. These included one each from the 1.5% halothane, 2.25% halothane, and reduced flow plus halothane groups.

Pharmacokinetic analysis of results from perfusions exposed to halothane, as well as results when flow was reduced, showed slower elimination of verapamil when compared with control values (Table

Table 1. Verapamil Pharmacokinetics Associated With Hepatic Perfusions In Vitro

	K_{el} (min^{-1})	AUC ($\mu g \cdot mL^{-1} \cdot min^{-1}$)
Control ($n = 6$)	0.27 ± 0.01	110.9 ± 4.2
1.5% halothane ($n = 5$)	0.23 ± 0.01^{a}	136.7 ± 9.1^{a}
2.25% halothane ($n = 5$)	0.18 ± 0.01^{a,b}	165.9 ± 7.4^{a,b}
Reduced hepatic flow ($n = 6$)	0.17 ± 0.01^{a,b}	172.7 ± 11.1^{a,b}
Reduced hepatic flow + 1.5% halothane ($n = 5$)	0.16 ± 0.00^{a,b}	192.4 ± 2.4^{a,b,c}

Results are shown as mean ± SEM.

AUC, area under the concentration-time curve; K_{el}, elimination-rate constant.

[a] Differs from control value ($P < 0.05$).

[b] Differs from 1.5% halothane value ($P < 0.05$).

[c] Differs from 2.25% halothane value ($P < 0.05$).

1). The elimination-rate constant (K_{el}) for the control group was found to be higher ($P < 0.05$) than for all other groups. The elimination-rate constant for perfusions receiving 1.5% halothane exposure was significantly higher than the 2.25% halothane, reduced flow, or the reduced flow with 1.5% halothane groups. There was no difference in K_{el} among either of the reduced flow groups or the 2.25% halothane group. Evaluation of the area under the concentration-time curve showed a pattern similar in terms of group differences to the results obtained for K_{el} with the control group having the lowest area under the concentration-time curve (AUC) (Table 1). Elimination curves for verapamil elimination in this system remained log-linear throughout all perfusions. Elimination curves for control, 1.5% halothane, and 2.25% halothane, shown in Figure 1, indicate a concentration-dependent influence of halothane on verapamil elimination. Reducing hepatic flow rate by 50% led to a decrease in the clearance of verapamil from the perfusate ($P < 0.05$) (Figure 2). The addition of 1.5% halothane to the reduced flow condition was associated with shifting of the verapamil clearance curve only slightly further to the right (Figure 2) and did not produce reduction in verapamil clearance.

Hepatic clearance of verapamil under the control conditions was higher than all other groups ($P < 0.05$) (Table 2). The hepatic clearance rate in 1.5% halothane-exposed perfusions was greater than in the 2.25% halothane-exposed liver, reduced flow, and reduced flow with halothane groups, which did not differ from each other.

Hepatic intrinsic clearance for verapamil in this system showed comparable values in both the control (85.7 mL/min) and reduced flow perfusions (83.9 mL/min). Intrinsic clearance in both the 1.5% and 2.25% halothane-exposed perfusions was lower than in the control and reduced flow perfusions ($P < 0.05$). The addition of 1.5% halothane to a 50% reduced flow resulted in a decrease in intrinsic clearance from 88.9 ± 12.9 to 72.68 ± 3.5 mL/min, which was not statistically significant.

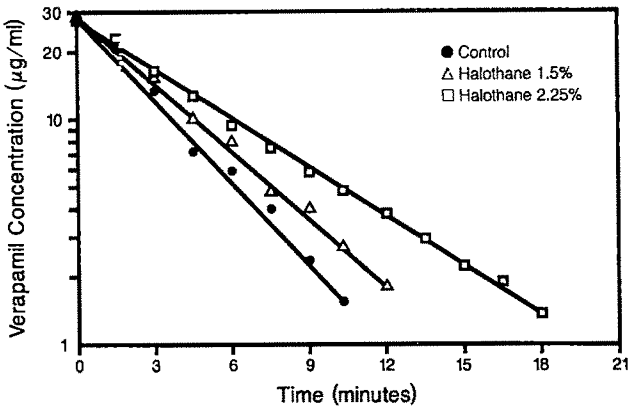

Figure 1. Semilogarithmic plot of reservoir perfusate verapamil concentrations versus time during control hepatic perfusions (●) and with perfusions equilibrated with 1.5% (△) and 2.25% (□) halothane showing concentration-dependent effect. Perfusate flow rate at 40 mL/min. Each curve represents five to six liver perfusions. Error bars are withheld for clarity.

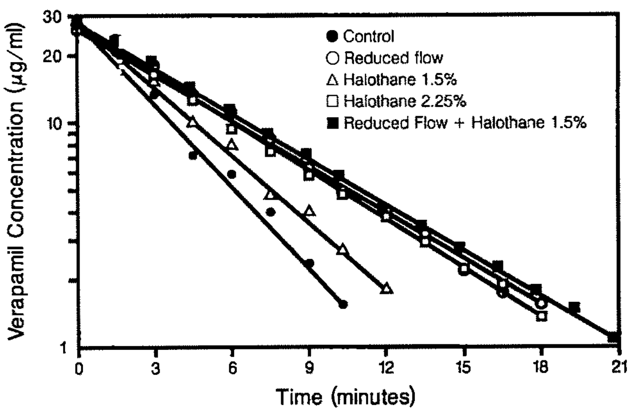

Figure 2. Semilogarithmic plot of reservoir perfusate verapamil concentrations versus time during control hepatic perfusions (●) and with perfusions equilibrated with 1.5% (△) and 2.25% (□) halothane, as in Figure 1. In addition, curves showing the effect of reduced flow by itself (○) and reduced flow with 1.5% halothane (■) at a 20-mL/min flow rate are included. Each curve represents five to six liver perfusions. Error bars are withheld for clarity.

Discussion

Results of this study indicate that both reduced hepatic blood flow and altered hepatic intrinsic clearance (hepatic enzyme metabolizing ability) influence verapamil clearance in the isolated perfused rat liver.

Table 2. Hepatic and Intrinsic Verapamil Clearance

	Hepatic clearance (mL/min)	Intrinsic clearance (mL/min)
Control ($n = 6$)	27.3 ± 1.0	85.7 ± 13.3[a]
1.5% halothane ($n = 5$)	23.1 ± 0.4[b]	54.9 ± 2.1[b]
2.25% halothane ($n = 5$)	17.6 ± 0.8[a,b]	31.9 ± 2.6[b,c]
Reduced flow ($n = 6$)	16.1 ± 0.8[a,b]	83.9 ± 12.6[a]
Reduced flow + 1.5% halothane ($n = 5$)	15.7 ± 0.2[a,b]	72.6 ± 3.5[a]

[a] Differs from 1.5% halothane value ($P < 0.05$).
[b] Differs from control value ($P < 0.05$).
[c] Differs from reduced flow + 1.5% halothane value ($P < 0.05$).

In this study we utilized an isolated perfused rat liver model that allowed maintenance of a constant hepatic perfusion during halothane administration. This system is valuable in that it permits separation of hepatic flow and hepatic enzyme inhibition properties with anesthetic administration; it will prove useful for evaluating other drug-drug interactions. The perfusate used for our study was devoid of added protein, and therefore effects such as alterations in protein binding could not be evaluated (12). Additionally, the hepatic perfusion rate that we utilized for our "reduced flow group" was necessarily chosen from previously obtained results in the literature. A flow reduction of 50% was chosen because previous results in vivo have shown a 40%–60% decrease in hepatic blood flow during 1.5–2 MAC (1.4%–2% in rats) halothane administration (6,7). Results of a previous study in dogs (5) indicate that intercompartmental clearance of verapamil was reduced, but also that an alteration in volume of distribution may have affected kinetics. Any influence of halothane on verapamil clearance caused by alterations in the volume of distribution would not be detected by our system because of its fixed volume of distribution.

Although decreased hepatic clearance was observed with a flow reduction of 50% in our system, it might be questioned whether this reduction in clearance could be due to hepatocellular hypoxia rather than to reduced drug delivery. Although higher flow rates are generally required when using perfusates deficient in red blood cells (2.7 $\text{mL}\cdot\text{g liver}^{-1}\cdot\text{min}^{-1}$), our lower flow state obtained this perfusion rate (average liver weight approximately 8 g). Additionally, there was no greater evidence of hepatic hypoxia on histologic examination in the reduced flow groups compared with livers perfused at 40 mL/min. Further evidence for the absence of hypoxia is found in the fact that intrinsic clearance of verapamil (enzyme-metabolizing ability) was not different between control and reduced flow groups. Our higher flow rate did not exceed 5 $\text{mL}\cdot\text{g liver}^{-1}\cdot\text{min}^{-1}$. Flow rates in excess of this rate may cause endothelial injury (11).

Evaluation of hepatic intrinsic clearance showed no differences between control and reduced flow groups. This is not unexpected: intrinsic clearance is a measure of hepatic enzyme-metabolizing ability and should be devoid of hepatic flow influences. The addition of halothane to the perfusate with hepatic flow rate constant at 40 mL/min showed a decrease in both hepatic and intrinsic clearances, a decrease that occurred in a dose-dependent fashion. Reduced flow of 50% caused a significant reduction in hepatic clearance compared with control. This result is consistent with the large effect alterations in hepatic flow have on the clearance of drugs, such as verapamil, with a high hepatic extraction ratio. The addition of 1.5% (1.5 MAC) halothane to a 50% reduced flow condition caused an alteration in intrinsic clearance from 83.9 to 72.7 mL/min; however, this was not a significant change. These results suggest that although enzyme-metabolizing inhibition may contribute to decreased clearance, the influence of the reduced hepatic perfusion that results during halothane administration may play a greater role.

The combination of high concentrations of halothane with elevated verapamil concentrations can result in profound decreases in cardiac ventricular function as well as depressed regional blood flows (3). This phenomenon is probably due to an interaction of the negative inotropic actions of halothane and verapamil in conjunction with the increased verapamil levels. Results of this study give some insight into the mechanisms by which verapamil clearance may be altered.

Data from this study, when combined with those of previous investigations (5), provide evidence that the elevated verapamil concentrations seen during halothane administration are most likely due to decreased total clearance as well as to a smaller contribution from anesthetic-induced changes in volume of distribution. Our data suggest that both decreased hepatic blood flow and decreased hepatic biotransformation may contribute to the component of decreased total verapamil clearance; however, a much larger contribution appears to be caused by the decrease in hepatic flow. Decreased verapamil doses during halothane administration may be required to prevent excessive plasma verapamil concentrations.

References

1. Reilly CS, Wood AJ, Koshakji RP, Wood M. The effect of halothane on drug disposition: contribution of changes in

intrinsic drug metabolizing capacity and hepatic blood flow. Anesthesiology 1985;63:70–6.

2. Reilly CS, Merrell J, Wood AJJ, Koshakji RP, Wood M. Comparison of the effects of isoflurane or fentanyl-nitrous oxide anaesthesia on propanolol disposition in dogs. Br J Anaesth 1988;60:791–6.
3. Chelly JE, Rogers K, Hysing ES, Taylor A, Hartley C, Merin RG. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. I. Verapamil and halothane. Anesthesiology 1986;64:560–7.
4. Rogers K, Hysing EJ, Merin RG, Taylor A, Hartley C, Chelly JE. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. II. Verapamil, enflurane, and isoflurane. Anesthesiology 1986;64:568–75.
5. Chelly JE, Hysing ES, Abernathy DR, Doursant M, Merin RG. Effects of inhalational anesthetics on verapamil pharmocokinetics in dogs. Anesthesiology 1986;65:266–71.
6. Gelman S, Fowler KC, Smith LR. Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 1984;61:726–30.
7. Hughes RL, Campbell D, Fitch W. Effects of enflurane and halothane on liver blood flow and oxygen consumption in the greyhound. Br J Anaesth 1980;52:1079–86.
8. Brown BR Jr. The diphasic action of halothane on the oxidative metabolism of drugs in the liver: in-vitro study in the rat. Anesthesiology 1971;35:241–6.
9. Frink EJ, Brown BR Jr. The effects of halothane, enflurane and isoflurane on the hepatic clearance of lidocaine and propanolol. Anesthesiology 1988;69:A454.
10. Harapat SR, Kates RE. High-performance liquid chromatographic analysis of verapamil. J Chromatogr 1980;181:484–9.
11. Gores GJ, Kost LJ, Nicholas LF. The isolated perfused rat liver: conceptual and practical considerations. Hepatology 1986;6:511–7.
12. Dale O, Gandolfi AJ, Brendel K, Schuman S. Rat liver slices and diazepam metabolism: in vitro interactions with volatile anaesthetic drugs and albumin. Br J Anaesth 1988;60:692–6.

Correlation of Train-of-Four and Double Burst Stimulation Ratios at Varying Amperages

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BRULL SJ, CONNELLY NR, SILVERMAN DG. Correlation of train-of-four and double burst stimulation ratios at varying amperages. Anesth Analg 1990;71:489–92.

The present study was undertaken to document the relationship between train-of-four (TOF) and double burst stimulation (DBS) at varying degrees of blockade, and to determine whether this relationship remained constant over a range of stimulating currents. The neuromuscular responses to the two most commonly employed modes of DBS stimulation, $DBS_{3,3}$ and $DBS_{3,2}$, and the responses to TOF nerve stimulation were recorded and compared at 20, 30, and 50 mA. Twenty-two consenting patients undergoing general anesthesia received a vecuronium infusion to achieve a TOF ratio within the range of 0.1–1.0. Train-of-four, $DBS_{3,3}$, and $DBS_{3,2}$ were delivered at 20, 30, and 50 mA in random sequence after a steady state of neuromuscular blockade was achieved. At a stimulating current of 50 mA, there was a significant linear correlation between $DBS_{3,3}$ and TOF ($P < 0.0001$; $r = 0.98$) over the range of blockade. Similarly, there was a high degree of correlation between $DBS_{3,2}$ and TOF at 50 mA, as the increased "fade" associated with $DBS_{3,2}$ was maintained throughout the spectrum of blockade ($P < 0.0001$; $r = 0.95$). The high degrees of correlation were maintained at stimulating currents of 20 and 30 mA ($P < 0.0001$). In conclusion, the present study revealed that there is a high degree of linear correlation between DBS and TOF, and that this mechanographic relationship is maintained over a wide range of stimulating currents during varying degrees of clinical neuromuscular blockade.

Key Words: MONITORING, NEUROMUSCULAR—train-of-four, double burst stimuli. NEUROMUSCULAR RELAXANTS, MONITORING.

Double burst stimulation (DBS) has been introduced as an alternative means of assessing neuromuscular blockade (1–4). $DBS_{3,3}$ consists of a minitetanic burst of three 200-μs impulses at a frequency of 50 Hz, followed 750 ms later by an identical burst. $DBS_{3,2}$ consists of a burst of three 200-μs impulses at 50 Hz followed 750 ms later by a burst of two such impulses (Figure 1). Double burst stimulation and train-of-four (TOF) stimulation maintain a close relationship over a wide degree of clinical blockade (1,4). To date, this relationship has been established at supramaximal, but not at submaximal, stimulating currents.

It recently has been reported that the ratio of the fourth twitch to the first twitch of TOF (i.e., T_4/T_1 ratio) remained consistent upon stimulation at 20, 30, and 50 mA. The consistency of adductor pollicis responses was demonstrated by intercurrent differences (i.e., differences in T_4/T_1 ratios obtained at varying stimulating currents) that were less than 3% (5). The nature of DBS stimulation (minitetanus) is quite different from that of TOF (single-twitch). This difference between the TOF and DBS stimuli, as well as the report that lesser currents are associated with less discomfort (6), makes defining the TOF to DBS relationship important for subsequent investigations and clinical applications. Because the literature is controversial with respect to which mode of DBS is more clinically useful in detecting neuromuscular fade by tactile means (1,2,4), both $DBS_{3,3}$ and $DBS_{3,2}$ were evaluated in the present study.

Materials and Methods

After approval by the institutional Human Investigational Committee, 22 consenting patients, ranging in age from 22 to 80 yr and free of known neuromuscular disease, were studied. Anesthesia was induced with thiopental (4–6 mg/kg), fentanyl (1–2 μg/kg), and midazolam (0.02–0.04 mg/kg), and was main-

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Received from the Department of Anesthesiology, Yale University School of Medicine, Yale-New Haven Hospital, New Haven, Connecticut. Accepted for publication July 16, 1990.

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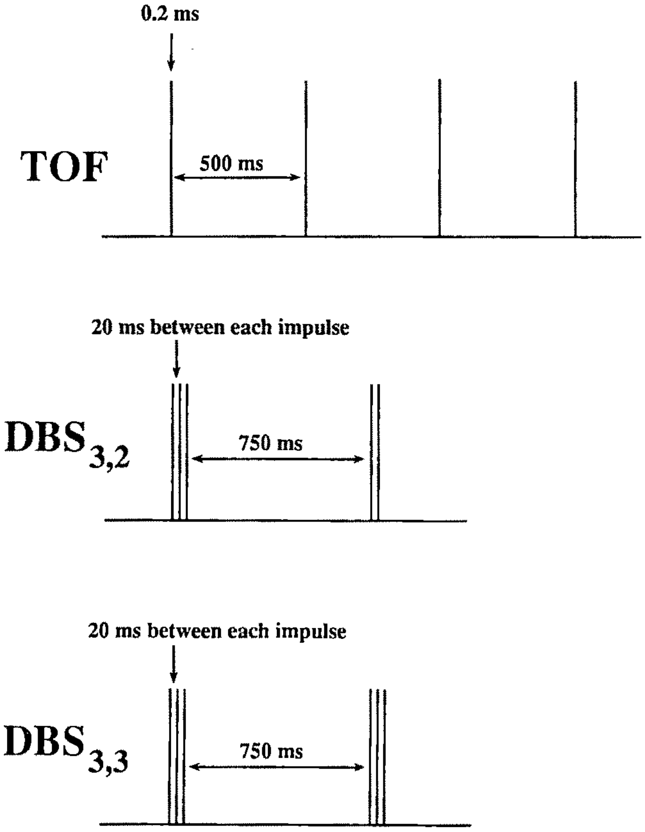
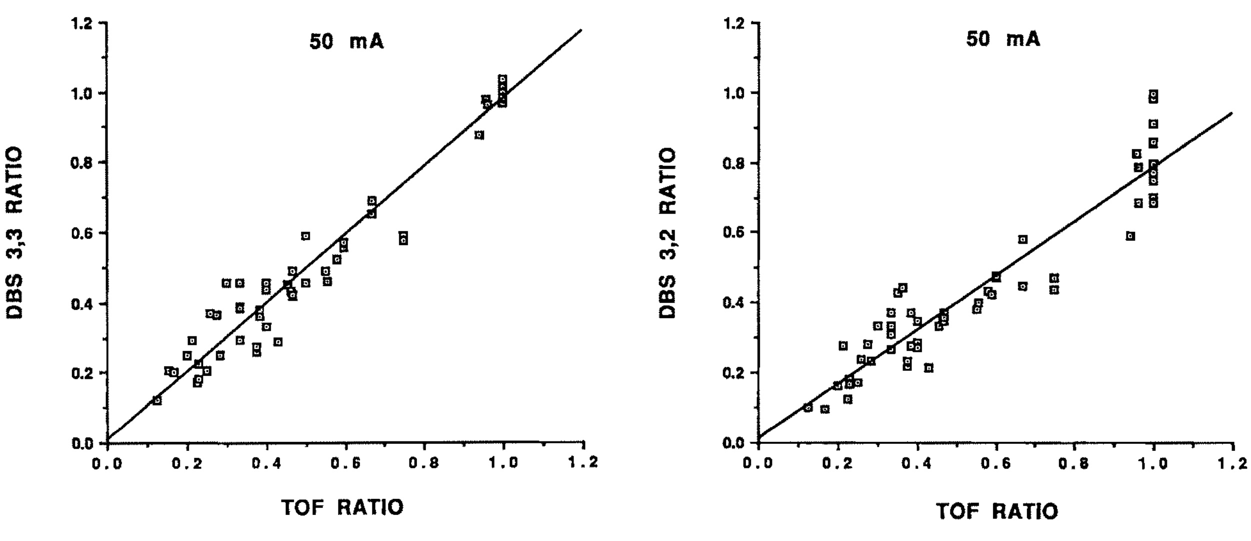


Figure 1. Illustration of TOF and DBS. All stimuli are 200 μs in duration, square-wave pattern, and of equal current intensity. Train-of-four consists of four stimuli at a frequency of 2 Hz. $DBS_{3,2}$ consists of three stimuli at 50 Hz followed 750 ms later by a burst of two stimuli at 50 Hz. $DBS_{3,3}$ consists of two groups of three stimuli at 50 Hz separated by 750 ms.

tained with isoflurane (0.25%–1.00% end-tidal) and 66% nitrous oxide (N_2O) in oxygen (O_2). The ulnar nerve was stimulated via cutaneous electrodes with a Myotest peripheral nerve stimulator (Biometer, Denmark). The output of the Myotest had been confirmed on an interfaced oscilloscope (Tektronix 7603, Tektronix, Inc., Beaverton, Ore.) at currents varying from 20 to 50 mA. The positive electrode was placed over the olecranon groove, and the negative electrode was placed on the volar aspect of the forearm (7,8). Thumb adduction in response to TOF stimulation every 10 s was quantified with an adductor pollicis force transducer (Myotrace APM-L, Professional Instruments, Houston, Tex.), which was interfaced to a monitor/stripchart recorder (Datascope 2000 A/2000 RS, Datascope Corp., Paramus, N.J.). Intubation was facilitated with intravenous succinylcholine (1–1.5 mg/kg).

When the height of the T_1 and T_4 responses to TOF stimulation at 50 mA had returned to the presuccinylcholine baseline, a continuous intravenous infusion of vecuronium was started to achieve a T_4/T_1 ratio between 0.1 and 1.0. Once the T_4/T_1 ratio (tested every minute) remained constant for at least 5 min, the responses to randomly delivered TOF, $DBS_{3,2}$, and $DBS_{3,3}$ stimulations were recorded at 20, 30, and 50 mA, with 20 s maintained between each stimulation. Once the neuromuscular responses to TOF and both modes of DBS were recorded at a particular current, a new degree of neuromuscular blockade was achieved by changing the vecuronium infusion rate, and new data were recorded as described above. An average of 2.5 data sets were obtained at different degrees of blockade in each subject, with at least a 15-min interval between sets. This provided a total of 50 sets of observations.

Figure 2. The correlation of the T_4/T_1 ratio to the D_2/D_1 ratio of $DBS_{3,3}$ ($r = 0.98$) and to the D_2/D_1 ratio of $DBS_{3,2}$ ($r = 0.95$) at 50 mA. The straight line represents the best-fit line.



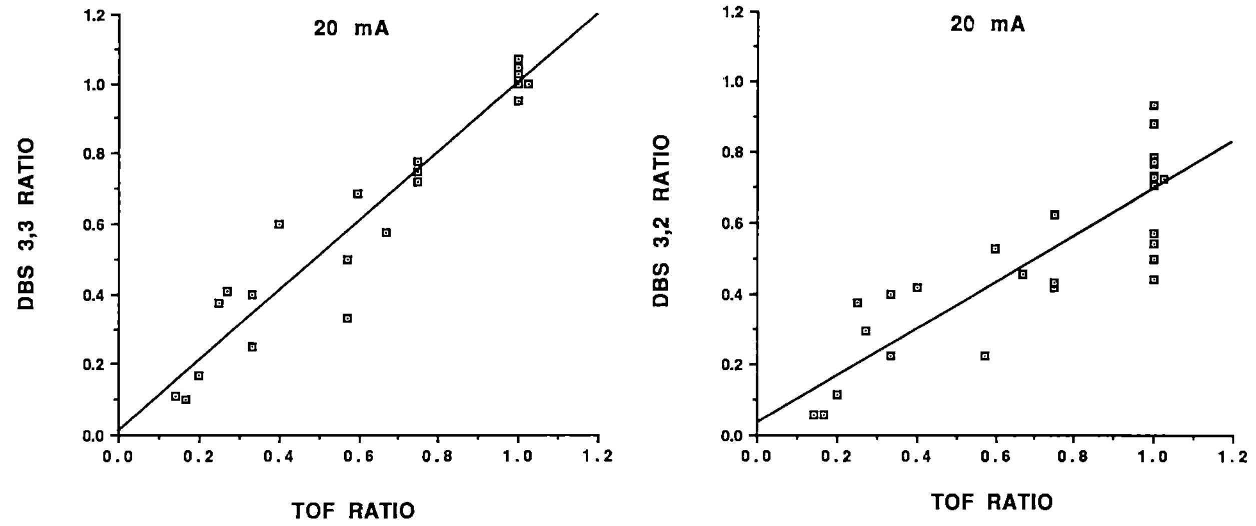


Figure 3. *Above* (*left and right*). The correlation of the T_4/T_1 ratio to the D_2/D_1 ratio of $DBS_{3,3}$ ($r = 0.97$) and to the D_2/D_1 ratio of $DBS_{3,2}$ ($r = 0.86$) at 20 mA. The straight line represents the best-fit line.

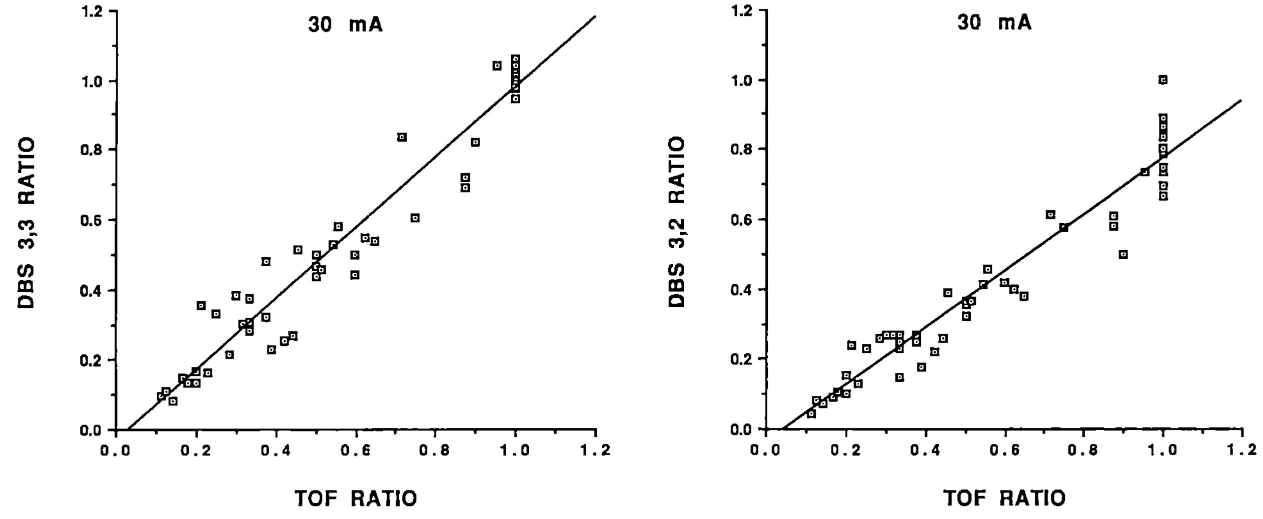


Figure 4. *Below* (*left and right*). The correlation of the T_4/T_1 ratio to the D_2/D_1 ratio of $DBS_{3,3}$ ($r = 0.98$) and to the D_2/D_1 ratio of $DBS_{3,2}$ ($r = 0.97$) at 30 mA. The straight line represents the best-fit line.

The heights of T_1, T_4, D_1, and D_2 were measured to the nearest millimeter and were estimated to a tenth of a millimeter. Then the ratios for TOF (T_4/T_1) and for DBS (D_2/D_1) were calculated. Data were analyzed with linear regression and expressed as mean ± SD. Differences were considered statistically significant at the $P < 0.05$ level.

Results

As shown in Figure 2, the data obtained at a supramaximal stimulating current of 50 mA documented the existence of a strong linear correlation between the T_4/T_1 ratio and the D_2/D_1 ratio of both $DBS_{3,3}$ and $DBS_{3,2}$ ($P < 0.0001$). This high degree of association was represented by r values of 0.98 for TOF versus $DBS_{3,3}$ and of 0.95 for TOF versus $DBS_{3,2}$. As the best-fit lines indicated (Figure 2), a T_4/T_1 ratio of 1.0 corresponded to a D_2/D_1 ratio of approximately 1.0 for $DBS_{3,3}$ and a ratio of 0.8 for $DBS_{3,2}$.

A significant linear correlation ($P < 0.0001$) also existed between the T_4/T_1 ratio and the D_2/D_1 ratios of both $DBS_{3,3}$ and $DBS_{3,2}$ at currents of 20 mA (Figure 3) and 30 mA (Figure 4). This correlation was represented for TOF versus $DBS_{3,3}$ by r values of 0.97 and 0.98 at stimulating currents of 20 and 30 mA, respectively. The correlation for TOF versus $DBS_{3,2}$ was demonstrated by r values of 0.86 and 0.97 at 20 and 30 mA, respectively.

Discussion

The present data indicated that the T_4/T_1 and the D_2/D_1 ratios were highly correlated at 20, 30, as well as at 50 mA. When comparable stimuli were delivered (i.e., T_1 and T_4 of TOF, and D_1 and D_2 of $DBS_{3,3}$), mechanographic assessment of TOF and $DBS_{3,3}$ both demonstrated a ratio of 1.0 in the absence of blockade, and similar fade throughout a clinically relevant range of neuromuscular blockade (i.e., T_4/T_1 of 0.1–1.0). The consistency of the ratio was maintained at submaximal as well as supramaximal currents.

As expected, in contrast to $DBS_{3,3}$, $DBS_{3,2}$ did not show a ratio of 1.0 in the absence of nondepolarizing neuromuscular blockade. The second burst of $DBS_{3,2}$ is of shorter duration than the first, to facilitate visual and tactile detection of fade (4); a T_4/T_1 ratio of 1.0 is associated with a $DBS_{3,2}$ D_2/D_1 ratio of approximately 0.8. Because it has been shown that significant fade (i.e., a T_4/T_1 ratio as low as 0.4) can go undetected visually or tactilely (9), it has been proposed that the built-in "fade" of $DBS_{3,2}$ will lessen the likelihood of premature extubation of the trachea. We elected to evaluate both forms of DBS, because they both correlate with TOF (3,5), and there is disagreement as to which form of DBS will prove to be superior (1,2,4).

The present confirmation that the relationship between TOF and DBS is maintained at less than supramaximal currents should facilitate subsequent applications and comparisons of these techniques. However, one should not conclude that visual or tactile assessment at lower currents would necessarily be comparable to the mechanographic assessment performed in the present investigation. It is possible that the decreased degree of contraction at lower currents would alter one's ability to detect fade in the absence of a mechanical recording device. It remains to be seen whether testing at lower currents will simply be a less painful means of evaluating fade when using a mechanical recording device, or whether it will prove to be a practical means of visually and/or tactilely assessing DBS or TOF neurostimulation.

The authors thank Theresa Z. O'Connor, MPH, for statistical analysis, and Paul G. Barash, MD, for reviewing this manuscript.

References

1. Engbaek J, Ostergaard D, Viby-Mogensen J. Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block. Br J Anaesth 1989;62:274–8.
2. Drenck NE, Ueda N, Olsen NV, et al. Manual evaluation of residual curarization using double burst stimulation: a comparison with train-of-four. Anesthesiology 1989;70:578–81.
3. Jones KA, Joyner MJ, Lennon RL. Visual and tactile evaluation of the response to double burst nerve stimulation (abstract). Anesthesiology 1989;71:A820.
4. Ueda N, Viby-Mogensen J, Olsen NV, Drenck NE, Tsuda H, Muteki T. The best choice of double burst stimulation pattern for manual evaluation of neuromuscular transmission. J Anesthesiol 1989;3:94–9.
5. Brull SJ, Ehrenwerth J, Silverman DG. Stimulation with submaximal current for train of four monitoring. Anesthesiology 1990;72:629–32.
6. Connelly NR, Brull SJ, O'Connor TZ, Silverman DG. Subjective responses to train-of-four and double burst stimulation in awake patients. Anesth Analg 1990;70:650–3.
7. Berger JJ, Gravenstein JS, Munson ES. Electrode polarity and peripheral nerve stimulation. Anesthesiology 1982;56:402–4.
8. Kopman AF, Lawson D. Milliamperage requirements for supramaximal stimulation of the ulnar nerve with surface electrodes. Anesthesiology 1984;61:83–5.
9. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemmer-Jorgensen B. Tactile and visual evaluation of the response of train-of-four nerve stimulation. Anesthesiology 1985;63:440–3.

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1990;71:493–7

Hemodynamic Effects of Diltiazem During Vasoconstrictor Pulmonary Hypertension in Sheep

Ronald G. Pearl, MD, PhD, and James C. Finn, MD

PEARL RG, FINN JC. Hemodynamic effects of diltiazem during vasoconstrictor pulmonary hypertension in sheep. Anesth Analg 1990;71:493–7.

Calcium channel blockers have been effective as pulmonary vasodilators in patients with pulmonary hypertension. The current study therefore compared the effects of prostaglandin E_1, an effective pulmonary vasodilator, with the effects of the water-soluble calcium channel blocker diltiazem during pulmonary hypertension in sheep. Pulmonary hypertension was produced by continuous intravenous administration of U46619 to halothane-anesthetized sheep. Prostaglandin E_1 decreased pulmonary artery pressure 29%, decreased pulmonary vascular resistance (Rp) 57%, and did not affect the ratio of pulmonary to systemic vascular resistance (Rp/Rs). Diltiazem decreased pulmonary artery pressure 15%, decreased Rp 50%, and did not affect Rp/Rs. When 0.33 mL/kg polyethylene glycol-ethanol vehicle (the vehicle used for nifedipine administration in a prior study) was administered during diltiazem infusion, pulmonary artery pressure increased 19%, Rp increased 72%, and Rp/Rs increased 29%. These results indicate that diltiazem is an effective pulmonary vasodilator and suggest that the previously reported unfavorable results of nifedipine may have been due to the vehicle used for nifedipine administration.

Key Words: LUNG, BLOOD FLOW—pulmonary hypertension. HORMONES, PROSTAGLANDIN—prostaglandin E_1, thromboxane, U46619. PHARMACOLOGY, DILTIAZEM, NIFEDIPINE.

Pulmonary hypertension increases right ventricular afterload and may therefore limit cardiovascular performance in acute and chronic cardiopulmonary disorders (1). Pulmonary vasodilator therapy may decrease pulmonary hypertension and result in hemodynamic and symptomatic improvement. However, pulmonary vasodilator therapy may produce excessive systemic vasodilation and result in systemic hypotension and right ventricular ischemia. The clinical efficacy of a pulmonary vasodilator may therefore be a function of the ratio of the changes in pulmonary and systemic vascular resistance (2,3). We have previously reported the effects of seven vasodilators (nitroglycerin, nitroprusside, hydralazine, prostaglandin E_1 [PGE_1], prostacyclin, isoproterenol, and nifedipine) during vasoconstrictor-induced pulmonary hypertension in sheep (4,5). With the exception of nifedipine, the hemodynamic effects of each agent were relatively consistent with the results reported in patients with pulmonary hypertension (2). Clinically, nifedipine has been an effective pulmonary vasodilator (6–9). However, in sheep, nifedipine resulted in a large increase (41%) in the ratio of pulmonary to systemic vascular resistance (Rp/Rs) and only a 2 mm Hg decrease in mean pulmonary artery pressure. Because nifedipine is not water-soluble, a polyethylene glycol-ethanol (PEG-EtOH) vehicle was used for nifedipine administration. Subsequent studies have demonstrated that small volumes (0.12 mL/kg) of a similar vehicle (40% propylene glycol) produce pulmonary hypertension in sheep (10). The PEG-EtOH vehicle in the prior study may therefore have contributed to the unfavorable pulmonary hemodynamic profile of nifedipine. Because all vehicles we have tried have produced pulmonary hypertension in sheep, we were unable to determine the hemodynamic effects of nifedipine alone. The current study was therefore designed to determine the effects of the water-soluble calcium channel blocker diltiazem, with and without the PEG-EtOH vehicle, during vasoconstrictor-induced pulmonary hypertension in sheep. To allow comparisons to our prior studies, the effects of PGE_1 were examined in the same sheep.

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from the Department of Anesthesia, Stanford University Medical Center, Stanford, California. Accepted for publication July 17, 1990.

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Methods

The protocol for this study was approved by the Stanford Panel on Laboratory Animal Care.

Six male sheep weighing 15–25 kg were anesthetized with 15–20 mg/kg thiopental IV. The sheep were intubated and mechanically ventilated using a tidal volume of 15–20 mL/kg and a rate adjusted to maintain arterial carbon dioxide tension between 35 and 45 mm Hg. Anesthesia was maintained with halothane (end-tidal concentration of 1%) in oxygen. Temperature was maintained at 37.5°–39°C with a warming blanket. After induction of anesthesia, systemic arterial, central venous, and triple-lumen pulmonary arterial catheters were inserted. Heart rate was measured by continuous electrocardiographic monitoring. One hour after catheter insertion, baseline measurements were obtained. Measured hemodynamic variables included heart rate (HR), mean systemic arterial pressure (Psa), right atrial pressure (Pra), mean pulmonary artery pressure (Ppa), pulmonary artery occlusion pressure (Ppao), and cardiac output (CO). Arterial and mixed venous blood gas samples were obtained. Pulmonary hypertension was then induced by continuous intravenous infusion of the vasoconstrictor U46619 (9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin F$_2\alpha$). The infusion rate was initially titrated until Ppa exceeded 30 mm Hg and CO was reduced by at least 25%; the infusion rate was then maintained constant for the duration of the experiment. Previous studies (4,5) have demonstrated that hemodynamics and pulmonary vascular reactivity remain stable for at least the next 4 h. Hemodynamic measurements (U46619-1) were obtained 30 min after beginning U46619. U46619 was continued, and PGE$_1$ was administered as a continuous intravenous infusion titrated to reduce Psa by 30%. Hemodynamic and blood gas measurements were obtained 15 min after a stable PGE$_1$ infusion rate had been obtained.

Prostaglandin E$_1$ was then discontinued. One hour later, a second set of measurements during U46619 administration (U46619-2) was obtained. U46619 was continued and diltiazem was administered as a continuous intravenous infusion titrated to decrease Psa by 30% (compared with the U46619-2 value). Hemodynamic and blood gas measurements were obtained 15 min after a stable diltiazem infusion rate had been obtained. Both U46619 and diltiazem were continued, and 0.33 mL/kg of the PEG-EtOH vehicle (15 g polyethylene glycol plus 15 g ethanol plus saline to a total volume of 50 mL) was administered over 5 min. A final set of hemodynamic and blood gas measurements was obtained.

Measurement Techniques

Intravascular pressures were measured at end-expiration with disposable pressure transducers (Trantec 53-600F) referenced to left atrial level and recorded on a Hewlett-Packard eight channel recorder. Cardiac output was determined in triplicate by thermodilution technique using 10 mL of room temperature saline injectate and an Edwards 9520A cardiac output computer. Blood gas tension levels and pH were analyzed using a Corning 168 pH/blood gas analyzer. Venous and arterial oxygen saturation values were calculated using a Severinghaus slide rule (11), assuming a P_{50} value of 27 mm Hg for sheep hemoglobin (12). Oxygen content (in mg/dL) was calculated as $C = (1.34 \times Hgb \times So_2) + (0.003 \times Po_2)$. Shunt fraction (Qs/Qt) was calculated as (capillary oxygen content − arterial oxygen content)/(capillary oxygen content − mixed venous oxygen content). Pulmonary vascular resistance (Rp; in dyne·s·cm^{-5}) was calculated as (Ppa − Ppao) × 80/CO; systemic vascular resistance (Rs; in dyne·s·cm^{-5}) as (Psa−Pra) × 80/CO; and stroke volume as CO/HR. The Rp/Rs ratio was calculated to assess the balance of pulmonary to systemic vasodilator effects.

Drugs

Prostaglandin E$_1$ and U46619 were gifts from Doug McCarter (Upjohn). U46619 stock solution (concentration 5 mg/mL) was prepared in absolute alcohol and stored at −20°C; aliquots of 0.4 mL were diluted in 50 mL saline for infusion. Prostaglandin E$_1$ was prepared in 0.2 M phosphate buffer at a concentration of 5 μg/mL. Diltiazem (Marion Laboratories) was dissolved in saline at a concentration of 0.3 mg/mL.

Statistics

Statistical analysis used repeated measures analysis of variance of the six time points (baseline, U46619-1, PGE$_1$, U46619-2, diltiazem, diltiazem + PEG-EtOH vehicle) followed by the Newman–Keuls multiple range test when appropriate. Probability values of <0.05 were considered significant. Results are reported as mean values ± standard error of the mean.

Results

U46619, infused at a rate of 1.05 ± 0.19 $\mu g \cdot kg^{-1} \cdot min^{-1}$, resulted in pulmonary hypertension. U46619 increased

Table 1. Hemodynamic and Oxygenation Variables During the Study

	Baseline	U46619-1	PGE_1	U46619-2	Diltiazem	Diltiazem/PEG-EtOH
Ppa (mm Hg)	10.3 ± 0.8	29.7 ± 1.1[a]	21.0 ± 1.0[a]	29.2 ± 1.2[a]	24.7 ± 1.0[a]	29.5 ± 1.2[a]
Psa (mm Hg)	88 ± 4	106 ± 4[a]	76 ± 2[a]	107 ± 4[a]	79 ± 3[a]	78 ± 2
Rp ($dyne \cdot s \cdot cm^{-5}$)	151 ± 28	1206 ± 209[a]	516 ± 121[a]	1238 ± 192[a]	620 ± 106[a]	1068 ± 170[a]
Rs ($dyne \cdot s \cdot cm^{-5}$)	2601 ± 162	5541 ± 1138[a]	2278 ± 386[a]	5846 ± 892[a]	2992 ± 339[a]	4008 ± 597
Rp/Rs	0.06 ± 0.01	0.22 ± 0.03[a]	0.22 ± 0.02	0.22 ± 0.02	0.21 ± 0.02[a]	0.27 ± 0.02[a]
CO (L/min)	2.6 ± 0.2	1.7 ± 0.3[a]	2.8 ± 0.4[a]	1.6 ± 0.2[a]	2.1 ± 0.3[a]	1.6 ± 0.3[a]
Ppao (mm Hg)	5.5 ± 0.3	7.8 ± 0.7[b]	5.3 ± 0.6[a]	7.3 ± 1.0[b]	9.8 ± 0.8[a]	10.5 ± 0.9
Pra (mm Hg)	4.2 ± 0.5	5.7 ± 0.4	3.8 ± 0.3	5.0 ± 0.9	7.2 ± 0.6[b]	7.7 ± 0.7
HR (beats/min)	119 ± 8	102 ± 9	126 ± 11[b]	102 ± 11[b]	83 ± 11[b]	78 ± 10
Pao_2 (mm Hg)	482 ± 24	434 ± 30	464 ± 30	424 ± 41	449 ± 32	449 ± 28
$P\bar{v}o_2$ (mm Hg)	67 ± 3	57 ± 6[b]	73 ± 4[a]	56 ± 6[a]	63 ± 4	57 ± 4
Qs/Qt	0.19 ± 0.02	0.17 ± 0.03	0.20 ± 0.02	0.16 ± 0.03	0.16 ± 0.01	0.14 ± 0.01

Values are given as mean ± SEM for six sheep.

PGE_1, prostaglandin E_1; Ppa, mean pulmonary artery pressure; Psa, mean systemic arterial pressure; Rp, pulmonary vascular resistance; Rs, systemic vascular resistance; CO, cardiac output; Ppao, pulmonary artery occlusion pressure; Pra, right atrial pressure; HR, heart rate; Pao_2, arterial oxygen tension; $P\bar{v}o_2$, mixed venous oxygen tension; and Qs/Qt, shunt fraction.

[a] $P < 0.01$ versus prior value.

[b] $P < 0.05$ versus prior value.

Ppa 188%, increased Rp 699%, increased Rp/Rs 267%, increased Psa 20%, and decreased CO 35% (Table 1). These effects of U46619 are similar to those reported in our previous studies (4,5). U46619 decreased $P\bar{v}o_2$ but did not significantly affect arterial Pao_2 or Qs/Qt. Prostaglandin E_1 infused at a rate of 59 ± 20 $ng \cdot kg^{-1} \cdot min^{-1}$, decreased Psa 28%, decreased Ppa 29%, decreased Rp 57%, decreased Rs 59%, increased CO 65%, and did not affect Rp/Rs (Table 1). These hemodynamic effects of PGE_1 are similar to those previously reported (4,5). Prostaglandin E_1 increased $P\bar{v}o_2$ and did not significantly affect Pao_2 or Qs/Qt.

After discontinuation of PGE_1, hemodynamic and blood gas variables were similar to those before PGE_1 (U46619-2 versus U46619-1). Diltiazem, infused at a rate of 70 ± 23 $\mu g \cdot kg^{-1} \cdot min^{-1}$, decreased Psa 26%, decreased Ppa 15%, decreased Rp 50%, decreased Rs 49%, increased CO 31%, and did not significantly affect Rp/Rs, Pao_2, $P\bar{v}o_2$, or Qs/Qt. Diltiazem significantly decreased HR and, in two sheep, resulted in second-degree heart block. Administration of PEG-EtOH vehicle during diltiazem administration increased Ppa 19%, increased Rp 72%, increased Rp/Rs 29%, and decreased CO 24%. Comparison of values during concomitant diltiazem-U46619-PEG-EtOH administration to values during U46619 administration alone (U46619-2) demonstrated no change in Ppa, a 27% decrease in Psa, a 14% increase in Rp, a 31% decrease in Rs, a 23% increase in Rp/Rs, and no change in CO.

Discussion

Pulmonary hypertension may occur as a primary disorder or may occur secondary to acute or chronic cardiac disease, pulmonary disease, or multiple systemic disorders (1). Increased pulmonary vascular resistance represents a decreased cross-sectional area of the pulmonary vascular bed. In general, this decrease involves both active vasoconstriction and structural remodeling of the pulmonary vascular bed. Active vasoconstriction has been demonstrated in primary pulmonary hypertension (13), adult respiratory distress syndrome (14), pulmonary embolism (15), hypoxia (16), and chronic obstructive lung disease (1). Pulmonary vasodilator therapy is designed to reverse this active vasoconstriction, thereby decreasing right ventricular afterload and improving CO. Potential adverse effects of pulmonary vasodilator therapy with calcium channel blockers are systemic hypotension due to systemic vasodilation and/or decreased myocardial contractility and hypoxia due to worsened ventilation-perfusion matching (17,18). Clinical studies of pulmonary vasodilator therapy have produced conflicting results, possibly due to individual patient variability over time (19), to heterogeneity among patients within a given etiology of pulmonary hypertension, and to heterogeneity of etiologies of pulmonary hypertension. Animal models of pulmonary hypertension have significant limitations, including marked hypoxemia (when hypoxia is used as the stimulus for vasoconstriction) and significant arterial obstruction (when thromboembolic models are used) (20). We therefore have studied vasodilator therapy in the current U46619 model in which pulmonary hypertension is due to active vasoconstriction.

U46619, a stable endoperoxide thromboxane A_2-mimetic, has potent effects on platelet aggregation and vascular smooth muscle contractility (21,22).

Thromboxanes have been implicated in a number of pathologic states characterized by abnormal vascular tone. Thromboxane A_2 has been associated with the pulmonary vasoconstriction occurring in association with sepsis (23), endotoxemia (24), complement activation (25), neutrophil activation (26), microembolism (27), and monocrotaline-induced pulmonary hypertension (28). In sheep, U46619 infusion has produced sustained pulmonary hypertension without excessive increases in systemic arterial pressure (4,5). Elevations in Ppa and Rp remain stable for at least 4 h. Vasodilator drug infusion can reduce Ppa and increase CO, indicating that reversible pulmonary vasoconstriction is present. U46619-induced pulmonary hypertension therefore appears to be a useful model for comparing the pulmonary vasodilator properties of drugs. This model has been effective in allowing assessment of the relative pulmonary and systemic hemodynamic effects of different clinically used pulmonary vasodilators (4,5).

Diltiazem has been used for clinical treatment of both primary and secondary pulmonary hypertension (6,29,30). In comparison to nifedipine, diltiazem has in general been less effective, possibly due to the decreased vasodilator effects and the increased negative inotropic, chronotropic, and dromotropic effects of diltiazem (31).

In the current sheep study, diltiazem was an excellent pulmonary vasodilator. Diltiazem decreased Ppa and Rp, and increased CO, despite decreasing HR. Diltiazem produced equal pulmonary and systemic vasodilation with no significant effect on the Rp/Rs ratio. The hemodynamic profile was similar to PGE_1, the most effective pulmonary vasodilator we have studied. The major differences between the two drugs (a larger increase in CO with PGE_1 than with diltiazem and a decrease in Ppao with PGE_1 versus an increase with diltiazem) were probably due to the negative chronotropic, inotropic, and dromotropic effects of diltiazem.

In our previous study on the effects of nifedipine in U46619-induced pulmonary hypertension (4), nifedipine decreased Rp by 34% but increased the Rp/Rs ratio by 41%. This hemodynamic profile was markedly inferior to the other six vasodilator drugs studied in this model (4,5). Subsequent to that study, we have described severe pulmonary hypertension as a consequence of propylene glycol administration in sheep (10). Propylene glycol-induced pulmonary hypertension could be prevented by thromboxane synthesis inhibition (10), consistent with thromboxane release from pulmonary intravascular macrophages in sheep (32). In our previous study with nifedipine, a PEG-EtOH vehicle was used for nifedipine administration. Thus, the adverse effects of nifedipine administration may have been related to the vehicle rather than to the drug. In the current study, the PEG-EtOH vehicle (when added to diltiazem) increased Ppa, Rp, and Rp/Rs. Comparison of the data from the previous study with the current study suggests that nifedipine (with PEG-EtOH vehicle) compared with diltiazem-PEG-EtOH resulted in a higher CO, a lower Ppa, a lower Rp, and a higher Rp/Rs, consistent with the greater vasodilator effects and less negative cardiac effects of nifedipine. It is, of course, impossible to quantify the effect of nifedipine itself separate from the vehicle. However, in the current study, diltiazem by itself was as effective as any of the six vasodilators previously studied, whereas the diltiazem-PEG-EtOH combination had no net pulmonary vasodilator activity. Thus, the prior report of pulmonary vasodilation with nifedipine (plus PEG-EtOH vehicle) suggests that nifedipine itself may be an effective pulmonary vasodilator in sheep. Studies of other calcium channel blockers in animal models appear to be indicated.

References

1. Harris P, Heath D. The human pulmonary circulation: its form and function in health and disease. 3rd ed. New York: Churchill Livingstone, 1986.
2. Packer M. Vasodilator therapy for primary pulmonary hypertension: limitations and hazards. Ann Intern Med 1985;103: 258–70.
3. Rich S, Martinez J, Lam W, Levy PS, Rosen KM. Reassessment of the effects of vasodilator drugs in primary pulmonary hypertension: guidelines for determining a pulmonary vasodilator response. Am Heart J 1983;105:119–27.
4. Prielipp RC, Rosenthal MH, Pearl RG. Hemodynamic profiles of prostaglandin E_1, isoproterenol, prostacyclin, and nifedipine in vasoconstrictor pulmonary hypertension in sheep. Anesth Analg 1988;67:722–9.
5. Prielipp RC, Rosenthal MH, Pearl RG. Vasodilator therapy in vasoconstrictor-induced pulmonary hypertension in sheep. Anesthesiology 1988;68:552–8.
6. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. Circulation 1987;76: 135–41.
7. Rubin LJ, Nicod P, Hillis LD, Firth BG. Treatment of primary pulmonary hypertension with nifedipine. A hemodynamic and scintigraphic evaluation. Ann Intern Med 1983;99:433–8.
8. Saadjian A, Philip-Joet F, Arnaud A. Hemodynamic and oxygen delivery responses to nifedipine in pulmonary hypertension secondary to chronic obstructive lung disease. Cardiology 1987;74:196–204.
9. Rubin LJ. Calcium channel blockers in primary pulmonary hypertension. Chest 1985;88:257S–9S.
10. Pearl RG, Rice SA. Propylene glycol-induced pulmonary hypertension in sheep. Pharmacology 1989;39:383–9.
11. Severinghaus JW. Blood gas calculator. J Appl Physiol 1966;21: 1108–16.

12. Altman P, Dittmer D. Blood and other body fluids. Washington, D.C.: Federation of American Societies for Experimental Biology, 1961:116.
13. Reeves JT, Groves BM, Turkevich D. The case for treatment of selected patients with primary pulmonary hypertension. Am Rev Respir Dis 1986;134:342–6.
14. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977;296:476–80.
15. Dantzker DR, Bower JS. Partial reversibility of chronic pulmonary hypertension caused by pulmonary thromboembolic disease. Am Rev Respir Dis 1981;124:129–31.
16. Carlsson AJ, Bindslev L, Hendenstierna G. Hypoxia-induced pulmonary vasoconstriction in the human lung. Anesthesiology 1987;66:312–6.
17. Packer M, Medina N, Yushak M. Adverse hemodynamic and clinical effects of calcium channel blockade in pulmonary hypertension secondary to obliterative pulmonary vascular disease. J Am Coll Cardiol 1984;4:890–901.
18. Packer M. Therapeutic application of calcium-channel antagonists for pulmonary hypertension. Am J Cardiol 1985;55:196B–201B.
19. Rich S, D'Alonzo GE, Dantzker DR, Levy PS. Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. Am J Cardiol 1985;55:159–63.
20. Herget J, Paleček F. Experimental chronic pulmonary hypertension. Int Rev Exp Pathol 1978;18:347–401.
21. Malmsten C. Some biological effects of prostaglandin endoperoxide analogues. Life Sci 1976;18:169–76.
22. Coleman RA, Humphrey PPA, Kennedy I, Levy GP, Lumley P. Comparison of the actions of U-46619, a prostaglandin H_2-analogue, with those of prostaglandin H_2 and thromboxane A_2 on some isolated smooth muscle preparations. Br J Pharmacol 1981;73:773–8.
23. Slotman GJ, Yellin SA, Handy JR, Hulstyn M, Husain SE, Gann DS. Thromboxane A_2 mediates hemodynamic and respiratory dysfunction in graded bacteremia. Surgery 1986;100: 214–21.
24. Brigham KL, Meyrick B. State of the art: endotoxin and lung injury. Am Rev Respir Dis 1986;133:913–27.
25. Gee MS, Perkowski SZ, Tahamont MV, Flynn JT, Wasserman MA. Thromboxane as a mediator of pulmonary dysfunction during intravascular complement activation in sheep. Am Rev Respir Dis 1986;133:269–73.
26. Loyd JE, Newman JH, English D, Ogletree ML, Meyrick BO, Brigham KL. Lung vascular effects of phorbol myristate acetate in awake sheep. J Appl Physiol 1983;54:267–76.
27. Malik AB. Pulmonary microembolism. Physiol Rev 1983;63: 1114–207.
28. Ganey PE, Ruth RA. 6-Keto prostaglandin $F_1\alpha$ and thromboxane B_2 in isolated, buffer-perfused lungs from monocrotaline pyrrole-treated rats. Exp Lung Res 1987;12:195–206.
29. Davidson A, Bossuyt A, Dab I. Acute effects of oxygen, nifedipine, and diltiazem in patients with cystic fibrosis and mild pulmonary hypertension. Pediatr Pulmonol 1989;6:53–9.
30. Clozel JP, Delorme N, Battistella P, Breda JL, Polu JM. Hemodynamic effects of intravenous diltiazem in hypoxic pulmonary hypertension. Chest 1987;91:171–5.
31. Young TE, Lundquist LJ, Chesler E, Weir EK. Comparative effects of nifedipine, verapamil, and diltiazem on experimental pulmonary hypertension. Am J Cardiol 1983;51:195–200.
32. Staub NC. Pulmonary intravascular macrophages. Chest 1988; 93(Suppl 3):84S–5S.

Pharmacokinetics and Pharmacodynamics of Doxacurium in Young and Elderly Patients During Isoflurane Anesthesia

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DRESNER DL, BASTA SJ, ALI HH, SCHWARTZ AF, EMBREE PB, WARGIN WA, LAI AA, BRADY KA, SAVARESE JJ. Pharmacokinetics and pharmacodynamics of doxacurium in young and elderly patients during isoflurane anesthesia. Anesth Analg 1990;71:498–502.

Preliminary disposition studies of the investigational, long-acting muscle relaxant doxacurium chloride (Nuromax) have demonstrated dual elimination by renal and hepatobiliary pathways, as well as slow hydrolysis by plasma cholinesterase. The present study compares the kinetics and dynamics of doxacurium in eight ASA physical status I or II elderly patients (67–72 yr of age) and eight ASA I or II young patients (22–49 yr of age). After institutionally approved written informed consent, kinetic and dynamic measurements were made after a 25-µg/kg bolus injection of doxacurium during 1.25 MAC nitrous oxide/oxygen/isoflurane anesthesia. Maximum twitch depression was similar in older patients (96.4% ± 1.3%) to that in the young patients (96.6% ± 1.8%). The time to achieve this level of block was significantly longer in the elderly than in the young (11.2 ± 1.1 min versus 7.7 ± 1.0 min, respectively). Recovery times to twitch heights of 5% and 25% of control tended to be prolonged and were more variable in the elderly (82.6 ± 17.2 and 97.1 ± 20.1 min, respectively) than in the young (54.8 ± 9 and 67.5 ± 8.2 min, respectively). Elimination half-life (96 ± 20 min) and clearance (2.47 ± 0.69 $mL \cdot kg^{-1} \cdot min^{-1}$) in the elderly patients were not statistically different from values found in the younger group. Volume of distribution at steady state in the elderly (220 ± 80.2 mL/kg) was significantly larger than in the young (150 ± 40.0 mL/kg). Renal excretion of unchanged drug was an important route of elimination, accounting for 24% of the dose in the elderly and 31% in the young. The observed pharmacokinetic and dynamic profile suggests that doxacurium may be given in a similar dosage regimen to both young and elderly patients.

Key Words: NEUROMUSCULAR RELAXANTS, DOXACURIUM. PHARMACOKINETICS, DOXACURIUM. PHARMACODYNAMICS, DOXACURIUM. AGE, DOXACURIUM PHARMACOKINETICS.

Differences in drug response and distribution are known to occur during the normal aging process (1–3). Decreased total body water and lean body weight, as well as a decreased serum albumin concentration with resulting decrease in protein binding, may each alter drug disposition in the elderly. Likewise, physiologic alterations in blood flow with decreased cardiac output, reduced delivery of drug via splanchnic circulation to the liver, and decreased renal blood flow and glomerular filtration rate may decrease elimination of drugs in the older population. Decreased elimination and longer duration of effect has been demonstrated with the long- and intermediate-acting muscle relaxants pancuronium (4,5), *d*-tubocurarine (6), metocurine (6), alcuronium (7), and vecuronium (8).

The present study compares pharmacokinetic and pharmacodynamic responses to the new, long-acting *bis*-benzylisoquinolinium diester relaxant doxacurium chloride (Nuromax) in elderly and young patients during isoflurane anesthesia. An additional purpose of the study was to ascertain whether urinary excretion of unchanged drug is a viable route of elimination, as has been suggested in early studies (9).

Received from the Department of Anesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts, and the Burroughs Wellcome Company, Research Triangle Park, North Carolina. Accepted for publication July 20, 1990.

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Methods

Approval was granted by the Subcommittee on Human Studies of the Massachusetts General Hospital. All patients gave written informed consent for all monitoring, data collection, doxacurium administration, and anesthetic procedures.

Sixteen ASA physical status I or II patients scheduled for elective orthopedic procedures were studied, eight elderly (67–72 yr of age) and eight young (22–49 yr of age). Age and weight for the elderly were 70 ± 2 yr and 76 ± 15 kg (mean ± SD), respectively; for the young, these were 31 ± 9 yr and 77 ± 17 kg, respectively. Women of childbearing potential were excluded, as were patients with a history of neuromuscular, cardiovascular, hepatic, or renal disorders. Patients who had been exposed to adrenal corticosteroids, phenytoins, barbiturates, or antihistamines were similarly excluded.

Subjects were premedicated with morphine (5–10 mg IM) and/or oral diazepam (5–15 mg) 1 h preoperatively. Anesthesia was induced with thiopental (3–5 mg/kg IV) and fentanyl (2–4 μg/kg IV) in divided doses. Controlled ventilation was established with oxygen and isoflurane given by mask. Intubation of the trachea was performed without the use of muscle relaxants. Blood pressure by oscillotonometry, electrocardiogram, oxygen saturation (Nellcor N-100 Pulse Oximeter), end-tidal isoflurane and $P\text{CO}_2$ (Puritan Bennett Analyzer), and temperature were monitored and recorded. Anesthesia was maintained at an end-tidal isoflurane concentration of 0.8% ± 0.1% with 60% nitrous oxide in oxygen (approximately 1.25 MAC of combined anesthetic gases). Ventilation was controlled throughout the study to maintain the arterial and/or end-tidal $P\text{CO}_2$ between 35 and 45 mm Hg. Esophageal temperature was kept between 35°C and 37°C by warming intravenous fluids, heated humidification of inspired gases, and adjustment of operating room temperature.

The mechanomyogram of thumb adduction was quantified with a Grass FT-10 force displacement transducer. Single twitch of the thumb was evoked at 0.15 Hz using supramaximal square-wave pulses 0.2 ms in duration, generated by a Grass S88 stimulator and applied through a stimulus isolation unit to the ulnar nerve at the wrist via two 23-gauge steel needle electrodes placed 3 cm apart. Train-of-four stimulation (2 Hz for 2 s) was applied during recovery from neuromuscular blockade. All measurements were recorded on a Grass model 7 polygraph.

Table 1. Neuromuscular Effects of Doxacurium

	Young ($n = 8$)	Elderly ($n = 8$)
Maximum block (%)	96.6 ± 1.8	96.4 ± 1.3
Time to 90% block (min)	5.7 ± 1.1	7.8 ± 0.7
Time to maximum block (min)	7.7 ± 1.0	11.2 ± 1.1^{a}
Begin recovery (min)	40.5 ± 6.4	44.8 ± 10.6
Time to 5% recovery (min)	54.8 ± 9.0^{b}	82.6 ± 17.2^{c}
Time to 25% recovery (min)	67.5 ± 8.2^{d}	97.1 ± 20.1^{d}

Values are expressed as mean ± SE.
$^{a}P < 0.05$ compared with the young group.
$^{b}n = 6$.
$^{c}n = 4$.
$^{d}n = 7$.

After stabilization of the baseline twitch response and achievement of a stable end-tidal isoflurane concentration, a single rapid intravenous bolus injection of doxacurium chloride (25 μg/kg) was given over 5 s. Blood pressure was taken every minute for the first 10 min after injection and every 5 min thereafter. Blood samples for determination of plasma concentration of doxacurium were drawn from a separate large-bore venous sampling catheter at 0, 2, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 min after injection. Urine was collected from seven patients (four elderly; three young) for up to 24 h to measure recovered doxacurium. All samples were analyzed by high-pressure liquid chromatography according to the method of DeAngelis et al. (10).

The plasma doxacurium concentration data were fitted to both two- and three-compartment models using an iteratively reweighted nonlinear least-squares regression program, NONLIN (11). The variance model in this regression analysis was the reciprocal of the concentration. Goodness of fit was assessed by the minimum sum of squares. Selection of an appropriate model to describe patient data was based on Akaike's Information Criterion (12). Pharmacokinetic parameters, including clearance (Cl) and volume of distribution at steady state (Vd_{ss}), were calculated according to standard equations based on statistical moments. Elimination half-life ($t_{1/2\ \beta}$) was determined by log linear regression analysis of the plasma doxacurium concentrations during the terminal phase. Comparisons between the young and the elderly were made using Student's t-test and analysis of variance, with a P value of less than 0.05 considered to be significant. Nonparametric analysis was made using the Kruskal–Wallis test.

Results

The neuromuscular effects of doxacurium are summarized in Table 1. Maximum block was 96.6% ± 1.8% for the young as compared with 96.4% ± 1.3%

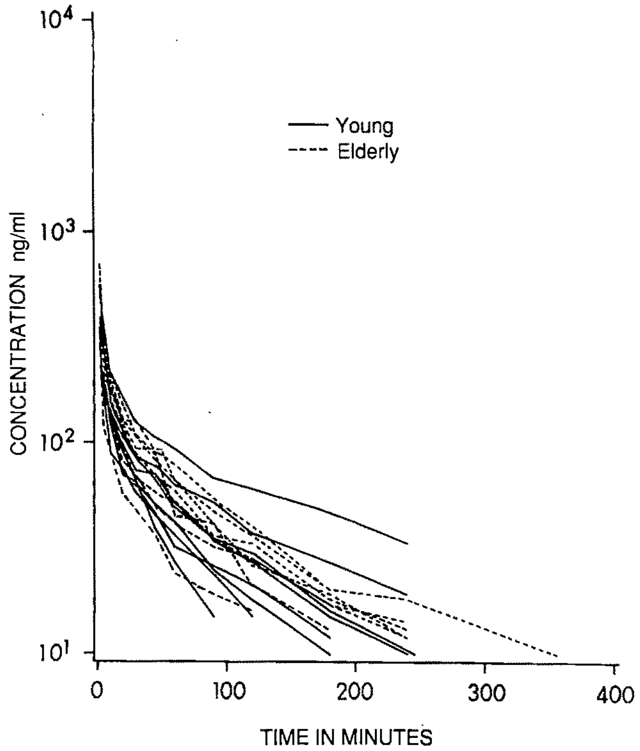

Figure 1. Individual patient plasma concentration-time profile after a 25-μg/kg bolus injection of doxacurium chloride.

Table 2. Pharmacokinetic Parameters for Doxacurium

	Young (n = 8)	Elderly (n = 8)
$t_{1/2\ \beta}$ (min)	86 ± 50	96 ± 20
Vd_{ss} (mL/kg)	150 ± 40	220 ± 80.2[a]
Cl (mL·kg^{-1}·min^{-1})	2.22 ± 1.09	2.47 ± 0.69

$t_{1/2\ \beta}$, elimination half-life; Vd_{ss}, volume of distribution at steady state; Cl, clearance.

Values are expressed as mean ± SD.

[a] $P < 0.05$ compared with the young group.

Table 3. Maximum Cardiovascular Changes From Preinjection Values During the First 5 Min After Doxacurium Administration

	Young		Elderly	
	Pre	Post	Pre	Post
Arterial pressure (mm Hg)	77 ± 2.8	75 ± 1.4	81 ± 4.0	84 ± 2.0
Heart rate (beats/min)	66 ± 2.5	67 ± 1.4	59 ± 2.6	57 ± 1.3

Pre, preinjection; post, postinjection.

Values are given as mean ± SE.

for the elderly. The time to maximum block was found to be significantly different in the elderly subjects (11.2 ± 1.1 min versus 7.7 ± 1.0 min in the young). The time until the beginning of recovery, 40.5 ± 6.4 min for the young, was not significantly different from that for the elderly (44.8 ± 10.6 min). Recovery times of twitch height to 5% and 25% of baseline tended to be more prolonged and demonstrated a larger variation in the elderly, although these were not statistically different from those in the young.

Individual plasma concentration decay curves, given in Figure 1, show a typical multicompartment elimination, with no apparent differences between the elderly and the young patient. Supportive evidence is shown in Table 2, which summarizes the pharmacokinetic results. Clearance and elimination half-life were similar in both patient groups. However, volume of distribution at steady state was found to be significantly larger in the elderly (220 ± 80.2 mL/kg) when compared with the young (150 ± 40.0 mL/kg).

Mean urinary excretion of unchanged doxacurium was 25% of the injected dose in the elderly patients, whereas 31% was recovered unchanged in the young.

No significant effect on mean arterial pressure or heart rate was seen in either the young or the elderly after doxacurium bolus injection. Mean pressure in the elderly varied from 81 ± 4 mm Hg preinjection to 84 ± 2 mm Hg postinjection, with a heart rate change of 59 ± 2.6 beats/min to 57 ± 1.3 beats/min. In the young, mean pressure varied from 77 ± 2.8 mm Hg preinjection to 75 ± 1.4 mm Hg postinjection, with a heart rate change of 66 ± 2.5 beats/min to 67 ± 1.4 beats/min (Table 3).

Discussion

The normal physiologic changes in organ function seen in the elderly do not appear to have a significant effect on the neuromuscular or pharmacokinetic properties of doxacurium with the exception of (a) slower onset time to maximum blockade; (b) slightly larger volume of distribution; and (c) a trend toward longer and more variable block duration in the elderly. Differences in initial fluid volume status, intraoperative blood loss, fluid replacement, and protein binding between the young and the elderly patients might account for the observed difference in volume of distribution at steady state. Initial fluid loading of the elderly was 1750 ± 707 mL (mean ± SD) as compared with the young (1063 ± 563 mL). Elderly subjects also sustained a larger average blood loss of 1637 mL (range, 125–4630 mL) as compared with their young counterparts (313 mL; range, minimal loss to

1800 mL). Total fluid replacement (5894 ± 3412 mL) was greater in the elderly than in the young (2588 ± 1816 mL). These differences were statistically significant ($P < 0.05$) and would tend to lower measured drug concentrations and elevate calculated volumes of distribution at steady state in the elderly. Such changes should not be expected to have a significant effect on the calculated plasma clearance of the drug. The unchanged clearance of doxacurium with a larger volume of distribution at steady state in the elderly population might explain the somewhat longer and more varied recovery times seen in this group. Review of individual patient results shows that the clinical duration of effect (injection to 25% recovery) was prolonged in some elderly patients (range, 35.6–178.7 min, versus 35.0–89.8 min in the young). This suggests that a subset of the elderly patients might be expected to experience a relatively long period of neuromuscular blockade. This observation is not easily explained by differences in age, estimated renal function (as measured by serum creatinine), or estimated pharmacokinetic parameters.

The decline of plasma doxacurium concentrations was best described as triphasic in some patients and biphasic in others. Hence, the selection of a unique two- or three-compartment model to describe the pharmacokinetics of doxacurium in humans cannot be made on the basis of present observations. Such kinetic behavior, although unusual, has also been observed with vecuronium (13).

Differences in drug distribution might be expected with bulky, charged structures characteristic of nondepolarizing muscle relaxants. After initial redistribution, these compounds are largely confined to the extracellular fluid compartment and typically have depended on urinary excretion for their elimination. The small mean Vd_{ss} of doxacurium (150–220 mL/kg) is consistent with the physicochemical properties of this large, polar compound with a molecular weight of over 1100 daltons. The mean plasma clearance for doxacurium (2.22–2.47 $mL \cdot kg^{-1} \cdot min^{-1}$) is comparable to published values for several long-acting nondepolarizing muscle relaxants including *d*-tubocurarine, gallamine, alcuronium, and pancuronium (14).

Well-documented decreases in glomerular filtration rate and renal plasma flow in the elderly have been linked to the prolonged elimination half-life and decreased clearance seen with long-acting neuromuscular blocking agents. Appropriate adjustments in dosage have been made on purely pharmacokinetic considerations, and have been supported with monitoring data using peripheral nerve stimulation (see below).

Matteo et al. (6) described markedly altered pharmacokinetic parameters for *d*-tubocurarine and metocurine in the elderly. In patients 70–87 yr of age, a decreased plasma clearance and volume of distribution, as well as a prolonged elimination half-life, was found when the data were compared with results in 29–59-yr-old patients. Likewise, recovery index was significantly longer in the elderly. However, no difference in the plasma concentration/twitch response relationship was found. The authors concluded that altered sensitivity to *d*-tubocurarine or metocurine could not explain these differences seen in the elderly; rather, age-related changes in the pharmacokinetics of the drugs seemed responsible.

Among the first to study the effects of age on the kinetics of muscle relaxants, McLeod et al. (4) demonstrated a decrease in plasma clearance of pancuronium with increasing age without corresponding differences in its volume of distribution. In fact, patients in the third decade of life cleared this relaxant twice as fast as those in the ninth decade. Later studies (5) showed a 35% decrease in plasma clearance of pancuronium and delayed urinary excretion in patients more than 75 yr old. Slower clearance resulted in a prolonged elimination half-life in the elderly. Duvaldestin et al. (5) also concluded that prolonged recovery times in the elderly were not due to changes in the pharmacodynamics of pancuronium because plasma concentration/response relationships in the elderly were comparable to observations in a younger group.

Studies with the intermediate-acting relaxant vecuronium have demonstrated a prolonged recovery index (8) and significantly lower plasma clearance and volume of distribution in the elderly. These changes can be explained by diminished total body water content and organ reserves in the elderly. Rupp et al. (15) showed that the $C_{pss_{50}}$—the steady state concentration of vecuronium that results in 50% paralysis—was similar in young and elderly patients. This observation supports unaltered pharmacodynamics of this drug in aging populations.

Atracurium is inactivated by Hoffman elimination and hydrolysis by nonspecific plasma esterases. Its elimination is largely organ-independent. As a result, age-related changes in kinetics or recovery times are not usually found (16,17). A later study (18) does suggest, however, that in a small elderly patient sample, age-related changes in protein binding might account for the measurement of a larger Vd_{ss}. This, together with a slightly greater nonorgan clearance and decreased organ clearance of atracurium, resulted in a longer elimination half-life. Kent et al. (19) showed no difference in clearance, volume of distribution, or mean residence time with atracurium in the elderly, although a clinically insignificant increase in elimination half-life was found. A different methodology could also explain these authors' rather unique results.

Preliminary studies with doxacurium suggest a significant hepatobiliary pathway for its elimination (Dresner DL, Basta SJ, Savarese JJ, et al., unpublished data). Biliary concentrations of doxacurium were 13–445 times higher than the plasma concentrations in five patients undergoing cholecystectomy. In vitro data have shown doxacurium to be a weak substrate for plasma cholinesterase (9). When enzyme-catalyzed rate of hydrolysis by human cholinesterase was estimated at high substrate concentrations, doxacurium hydrolysis occurred at 6% the rate of succinylcholine.

Although the relative roles of renal elimination, biliary excretion, and enzymatic hydrolysis of doxacurium in plasma have yet to be clarified, all these routes may be operative in human subjects. The similar neuromuscular blocking effects and kinetics of doxacurium in young and elderly patients may be due to these several influences on drug clearance. The data in the present study suggest that the dosage of doxacurium in elderly patients is similar to regimens used in younger populations.

References

1. George CF. Drug kinetics and hepatic blood flow. Clin Pharmacokinet 1979;4:433–48.
2. Davies D, Shock N. Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. J Clin Invest 1950;29:496.
3. Richey DP, Bender AD. Pharmacokinetic consequences of aging. Ann Rev Pharmacol Toxicol 1977;17:49–65.
4. McLeod K, Hull J, Watson MJ. Effects of ageing on the pharmacokinetics of pancuronium. Br J Anaesth 1979;51:435.
5. Duvaldestin P, Saada J, Berger JL, D'Hollander A, Desmonts JM. Pharmacokinetics, pharmacodynamics, and dose-response relationships of pancuronium in control and elderly subjects. Anesthesiology 1982;56:35–40.
6. Matteo RS, Backus WW, McDaniel DD, Brotherton WP, Abraham R, Diaz J. Pharmacokinetics and pharmacodynamics of *d*-tubocurarine and metocurine in the elderly. Anesth Analg 1985;64:23–9.
7. Stephens ID, Ho PC, Holloway AM, Bourne DWA, Triggs EJ. Pharmacokinetics of alcuronium in elderly patients undergoing total hip replacement or aortic reconstructive surgery. Br J Anaesth 1984;56:465.
8. D'Hollander A, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose-response relationship of Org NC45 in anaesthetized patients. Br J Anaesth 1982;54:653–6.
9. Basta SJ, Savarese JJ, Ali HH, et al. Clinical pharmacology of doxacurium chloride. Anesthesiology 1988;69:478–86.
10. DeAngelis R, Maehr R, Savarese J, Welch R. Liquid chromatographic analysis of doxacurium, a new long-acting neuromuscular blocker. J Chromatogr Biomed Appl 1990;525:389–400.
11. Metzler CM, Elfring GL, McEwen AJ. A package of computer programs for pharmacokinetic modeling. Biometrics 1974;30: 562.
12. Yamaoka K, Nakagawa T, Uno T. Application of Akaike's Information Criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharmacol 1978;6: 165–75.
13. Bencini AF, Scaf AHJ, Sohn YJ, et al. Hepatobiliary disposition of vecuronium bromide in man. Br J Anaesth 1986;58:988–95.
14. Ramzan MI, Somogyi AA, Walker JS, et al. Clinical pharmacokinetics of the non-depolarizing muscle relaxants. Clin Pharmacokinet 1981;6:25–60.
15. Rupp S, Fisher DM, Miller RD, Castagnoli K. Pharmacokinetics and pharmacodynamics of vecuronium in the elderly. Anesthesiology 1983;59:A270.
16. D'Hollander AA, Luyckx C, Barvais L, De Ville A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. Anesthesiology 1983;59:237–40.
17. De Bros F, Okutani R, Lai A, Lawrence KW, Basta S. Pharmacokinetics and pharmacodynamics of atracurium in the elderly. Anesthesiology 1987;67:A604.
18. Kitts JB, Fisher DM, Canfell PC, et al. Pharmacokinetics and pharmacodynamics of atracurium in the elderly. Anesthesiology 1990;72:272–5.
19. Kent AP, Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in the elderly. Br J Anaesth 1989;63: 661–6.

Changes in Cerebral Blood Flow Velocity After Release of Intraoperative Tourniquets in Humans: A Transcranial Doppler Study

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HIRST RP, SLEE TA, LAM AM. Changes in cerebral blood flow velocity after release of intraoperative tourniquets in humans: a transcranial Doppler study. Anesth Analg 1990;71:503–10.

The effect of release of intraoperative thigh tourniquets on velocity of blood flow in the middle cerebral artery was examined in five patients given general anesthesia with controlled ventilation for lower extremity orthopedic procedures using transcranial Doppler sonography. Middle cerebral artery blood flow velocity increased significantly from 52 ± 6 (SEM) to 82 ± 24 cm/s (an increase of 58% ± 13%) within 4 ± 1 min after tourniquet release and remained significantly elevated for 7 min. A positive linear correlation was found between middle cerebral artery blood flow velocity and P_{ETCO_2} *on each occasion* $(0.97 \geq r \geq 0.84, 0.001 > P > 0.0001)$ *after tourniquet deflation. Assuming a linear relationship between flow velocity and flow, these findings suggest that significant increase in cerebral blood flow can occur after intraoperative tourniquet release and that this increase appears to be mostly* CO_2*-dependent.*

Key Words: BRAIN, BLOOD FLOW—tourniquet release. EQUIPMENT, TOURNIQUETS—cerebral blood flow after release.

Pneumatic tourniquets are commonly used during orthopedic procedures on the extremities to provide a bloodless surgical field. While the tourniquet is inflated, metabolic changes occur in the ischemic limb, changes that include increased Pa_{CO_2}, lactic acid, and potassium, and decreased levels of Pa_{O_2} and pH (1–5). Deflation of the tourniquet results in the release of these products of ischemia into the general circulation. The resultant decreases in arterial pH and Pa_{O_2} and increases in arterial lactic acid, potassium, Pa_{CO_2}, and P_{ETCO_2} (5–10) are associated with significant decreases in mean arterial and central venous pressures and increases in heart rate (6,9,11). The clinical significance of these changes is not yet clear, even though in healthy individuals no significant adverse effects have been observed.

In normal patients the role of Pa_{CO_2} as a major regulator of cerebral vasomotor tone has been well studied. Elevations of Pa_{CO_2} result in cerebral vasodilation and increased cerebral blood flow (CBF), whereas lowering Pa_{CO_2} has the reverse effect. The rapid increase in Pa_{CO_2} after thigh tourniquet release would be expected to result in a corresponding increase in CBF. Although this transient increase in CBF is well tolerated in otherwise healthy patients, the concomitant increase in cerebral blood volume may cause an increase in intracranial pressure (ICP) in patients with intracranial space-occupying lesions and decreased intracranial compliance. Indeed severe increases in ICP after tourniquet release recently have been reported in such patients (12,13). The increase in ICP, coupled with a simultaneous decrease in systemic blood pressure, could lead to a severe reduction in cerebral perfusion pressure with potentially disastrous consequences.

In the present study, changes in middle cerebral artery (MCA) blood flow velocity after tourniquet release using transcranial Doppler sonography (TCD) were measured in five normal patients undergoing orthopedic procedures on the lower extremity requiring the use of a tourniquet. The purpose of the study was twofold: (a) to test the hypothesis that the release of thigh tourniquets during orthopedic procedures significantly increases MCA blood flow velocity; and

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Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington. Accepted for publication July 24, 1990.

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(b) to characterize the time-course of the change in MCA flow velocity in relationship to the change in $\mathrm{P_{ET}CO_2}$.

Methods

The study was approved by the Human Subjects Review Committee of the University of Washington. Five ASA physical status I patients, aged 28–60 yr, free of neurologic and cerebrovascular diseases, who were undergoing orthopedic procedures requiring the use of a tourniquet on the lower extremity, were studied. Patient 1 had a tourniquet applied to both legs consecutively; each was released at a different time, and data were collected after each release and treated separately.

Anesthetic induction was carried out with 4–5 mg/kg thiopental and 2–3 μg/kg fentanyl or 25 μg/kg alfentanil, followed by 1 mg/kg succinylcholine or 0.1 mg/kg vecuronium. After tracheal intubation, ventilation was controlled and adjusted to maintain $\mathrm{P_{ET}CO_2}$ between 30 and 38 mm Hg with tidal volume between 10 and 12 mL/kg and respiratory rate of 8–10 per minute. End-tidal carbon dioxide pressure was measured continuously with a capnograph (Spacelab, Redmond, Wash.). Anesthesia was maintained with isoflurane (0.5%–1.5% inspired), 60% N_2O, and vecuronium as required; most patients also received an infusion of fentanyl or alfentanil (Table 1). Other monitoring included pulse oximetry, electrocardiogram, and noninvasive blood pressure measurement with oscillometry.

The TCD (Medasonics, Mountainview, Calif.) probe that transmits a 2-MHz pulsed wave was positioned over the left temporal bone window and anchored using a head harness so that the angle of insonation remained constant throughout the study. Doppler signals from the left MCA were identified and measured at a depth of 45 mm. The shift in frequency spectra of the Doppler signals converted into velocity was displayed on a video monitor and peak systolic and diastolic MCA flow velocities in centimeters per second were obtained by manually manipulating the cursor to read the average value from two to three cardiac cycles. When respiratory fluctuations were evident, care was taken to obtain the values only during end-expiration. The time-mean velocity, considered to be the most physiologic measure of flow velocity (14), is normally displayed by the equipment in a continuous manner. This function, however, was rendered inaccurate during intraoperative recordings because of artifacts generated from the electrocardiogram. Mean MCA flow velocity was therefore calculated from systolic and diastolic velocities using the following formula: mean MCA flow velocity = (systolic velocity − diastolic velocity)/3 + diastolic velocity.

Baseline measurements of blood pressure, heart rate, and systolic and diastolic MCA velocities with stable $\mathrm{P_{ET}CO_2}$ were established immediately before tourniquet release. Tourniquet pressure was 300 mm Hg, for each procedure, and the duration of inflation was recorded. After release of the tourniquet, blood pressure, heart rate, systolic and diastolic MCA flow velocities, and $\mathrm{P_{ET}CO_2}$ were measured every minute for 10 min or until the MCA flow velocity had returned to within 10%, and $\mathrm{P_{ET}CO_2}$ was within 2 mm Hg, of their respective baseline values. During the measurement periods, tidal volume and minute ventilation were maintained unchanged.

For statistical analysis one-way analysis of variance for repeated measures was used. Where significant differences were found, a multiple comparison procedure (Tukey's test) was used for further analysis. A P value of less than 0.05 was considered statistically significant. Linear regression analysis was used for comparing changes in MCA blood flow velocity with changes in $\mathrm{P_{ET}CO_2}$. All values are expressed as mean ± SEM unless otherwise specified.

Results

Patient characteristics, including age, weight, sex, type of surgery, type of anesthesia, and tourniquet inflation times, are summarized in Table 1. Mean MCA blood flow velocity increased within 2 min of tourniquet deflation and reached a maximum of 82 ± 24 cm/s in 4 ± 1 min (Figure 1). This represents a 58% ± 13% increase above baseline values. Although the increase in mean MCA blood flow velocity reached statistical significance only from 2 to 7 min, it remained above baseline when the study was terminated at 10 min (Figure 1). (In two of the six studies, the MCA flow velocity did not return to within 10% of baseline until after 15 min. These two patients also had elevated $\mathrm{P_{ET}CO_2}$ for similar durations: see below.) There was a correspondingly rapid increase in $\mathrm{P_{ET}CO_2}$ after tourniquet release. The time-course of the mean $\mathrm{P_{ET}CO_2}$ after tourniquet deflation is displayed in Figure 2. The increase was most rapid within 1 min of deflation. The maximum level of $\mathrm{P_{ET}CO_2}$ achieved, 44 ± 5 mm Hg (an increase of 34% ± 12%), occurred 2 ± 0.4 min after release. The mean time for $\mathrm{P_{ET}CO_2}$ to return to within 2 mm Hg of baseline was 8 ± 1 min except in two patients, in whom $\mathrm{P_{ET}CO_2}$ did not satisfy this criterion until 14 and 19 min. Both patients

Table 1. Patient Profile

Patient	Age (yr)	Weight (kg)	Sex	Surgery	Anesthesia	Duration of tourniquet inflation (min)
1	41	90	M	Bilateral ankle ORIF	ISF (0.5%), N_2O, fentanyl infusion	Right: 77; Left: 104
2	42	71	M	Right calcaneus ORIF	ISF (1.5%), N_2O	121
3	30	45	F	Right ankle ORIF	ISF (0.75%), N_2O, fentanyl infusion	120
4	60	90	F	Left foot revision Triple arthrodesis	ISF (0.75%), N_2O, fentanyl infusion	60
5	28	70	M	Right ankle arthroscopy	ISF (0.5%), N_2O, alfentanil	66

ORIF, open reduction and internal fixation; ISF, isoflurane; N_2O, nitrous oxide.

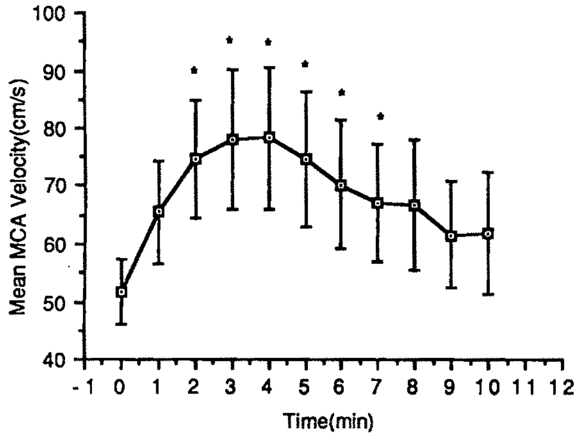

Figure 1. Mean MCA flow velocity values after tourniquet release at time 0. Middle cerebral artery flow velocity peaked at about 4 min and remained significantly above baseline values from 2 to 7 min ($P < 0.05$). *$P < 0.05$ vs time 0. Bars indicate standard error of the mean.

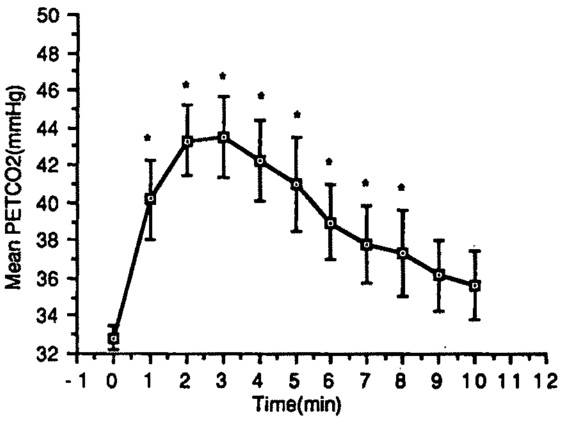

Figure 2. End-tidal carbon dioxide pressure levels after tourniquet release at time 0. End-tidal carbon dioxide pressure peaked around 2 min and remained significantly above baseline values from 1 to 8 min ($P < 0.05$). *$P < 0.05$ vs time 0. Bars indicate standard error of the mean.

had tourniquets inflated for more than 90 min (104 and 120 min, respectively). The difference between the time to maximum Petco$_2$ and the maximum mean MCA blood flow velocity was statistically significant ($P = 0.025$, unpaired t-test). Maximum changes and times of occurrences of these peaks are shown in Table 2.

Significant hemodynamic changes also occurred after tourniquet deflation: heart rate increased by a maximum of 8 ± 3 beats/min ($P < 0.005$, paired t-test), but the transient increase over time did not reach statistical significance ($P = 0.06$, analysis of variance with repeated measures) (Figure 3), and there was an immediate decline in mean blood pressure. The decrease in blood pressure was statistically significant only for the first 4 min, although blood pressure remained below baseline values at the end of the study (Figure 4).

A strongly positive correlation between mean MCA flow velocity and Petco$_2$ determined by linear regression analysis was demonstrated in all six studies ($0.97 \geq r \geq 0.84$, $0.001 > P > 0.0001$). A representative plot is shown in Figure 5. The mean slope, calculated from each linear regression slope expressed as a percentage of the velocity at Petco$_2$ of 40 mm Hg, is 3.3% ± 0.6% mm Hg^{-1} of Petco$_2$. When each MCA flow velocity data point is normalized in the same fashion, i.e., expressed as a percentage of the velocity at Petco$_2$ of 40 mm Hg as determined by individual linear regression analysis, and plotted against the respective Petco$_2$, a strong linear relationship is again obtained, with a slope of 3.2% (Figure 6), essentially the same as the value obtained by averaging the individual slopes. Such normalization is necessary because there is considerable variation in MCA flow velocity as well as in Petco$_2$ values before tourniquet release.

The relationship between tourniquet time and maximum percent change in mean MCA flow velocity and maximum Petco$_2$ was also compared using linear regression analysis. There was no correlation between tourniquet time and maximum percent change in mean MCA flow velocity ($r = 0.176$, $P = 0.74$). A weakly positive correlation was observed

Table 2. Mean Middle Cerebral Artery Flow Velocity Values and PETCO$_2$ Before and After Tourniquet Deflation

Variables	Mean ± SEM
MCA flow velocity before release (cm/s)	52 ± 6
Maximum MCA flow velocity after release (cm/s)	82 ± 12^a
Maximum increase in MCA flow velocity (%)	58 ± 13^a
Time to maximum MCA flow velocity (min)	4 ± 0.4^b
Time for MCA flow velocity to return to within 10% of baseline levels (min)	6.8 ± 1^c
Baseline PETCO$_2$ (mm Hg)	33 ± 2
Maximum PETCO$_2$ (mm Hg)	44 ± 5^a
Maximum increase in PETCO$_2$ (%)	34 ± 12
Time to maximum PETCO$_2$ (min)	2 ± 0.4^b
Time for PETCO$_2$ to return to within 2 mm Hg of baseline (min)	8 ± 1^c

MCA, middle cerebral artery; PETCO$_2$, end-tidal carbon dioxide pressure.
^{a}$P < 0.05$ versus baseline.
^{b}Statistically significant ($P = 0.025$) difference between time to maximum mean MCA velocity and time to maximum PETCO$_2$.
^{c}$n = 4$; two patients did not meet these criteria until 15 and 18 min for MCA velocity, and 14 and 19 min for PETCO$_2$, respectively.

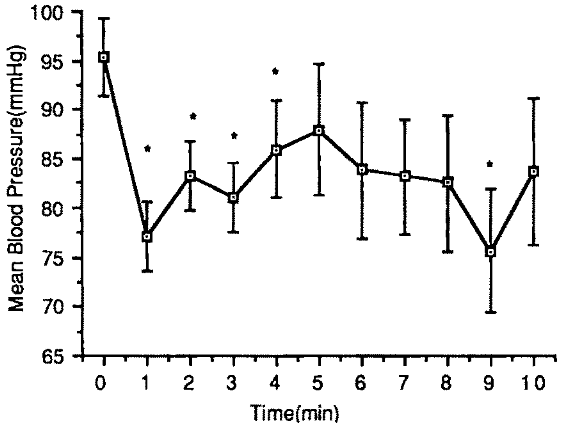

Figure 3. Mean arterial blood pressure values after tourniquet release at time 0. The immediate decrease in mean arterial blood pressure remained statistically significant for 4 min. There was no apparent explanation for the dip at 9 min. *$P < 0.05$ vs time 0. Bars indicate standard error of the mean.

between tourniquet time and maximum percent change in PETCO$_2$ ($r = 0.678$, $P = 0.14$).

Discussion

Our data show a dramatic increase in MCA flow velocity after tourniquet release, an increase that correlates strongly with the increase in PETCO$_2$. The changes in PETCO$_2$ after tourniquet release were similar to what have been observed in previous studies (8–10). There appears to be a time lag between the increase in PETCO$_2$ and the increase in MCA flow velocity as demonstrated by the significant difference between time to peak PETCO$_2$ and time to peak MCA flow velocity. This is also observable by comparing the shape of the curves when PETCO$_2$ is plotted against time and when MCA flow velocity is plotted against time in Figures 1 and 2. Despite this, the two variables were positively related in a linear fashion (Figures 5 and 6). We interpret this to mean that CBF increases significantly after tourniquet release, and most if not all of this increase can be accounted for by the concomitant increase in CO$_2$.

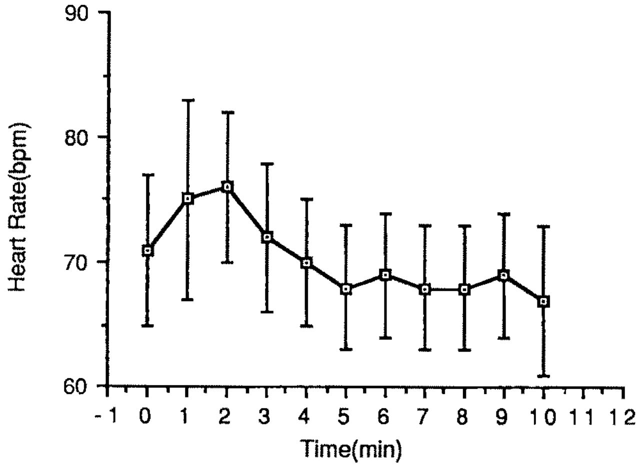

Figure 4. Heart rate values after tourniquet release at time 0. Because of variation of the baseline heart rate between subjects, the transient increase did not reach statistical significance ($P = 0.06$). The maximum increase of 8 beats/min was significant ($P < 0.005$). Bars indicate standard error of the mean.

The validity of measuring MCA blood flow velocity as an index of CBF needs comment. This noninvasive technique of measuring CBF velocity was first introduced by Aaslid et al. in 1982 (15). The main assumption is that the caliber of the MCA is constant during changes in PETCO$_2$. Because blood flow is equal to the product of instantaneous flow velocity and the cross-sectional area of the vessel, a change in vessel diameter could have a significant effect on flow velocity. Available evidence suggests that the assumption is probably valid (16), although questions have been raised regarding the influence of blood pressure changes on the diameter of these cerebral arteries (17). Angiographic evidence suggests the caliber of the large basal cerebral arteries remains constant during changes in Paco$_2$ (18). Moreover, studies of cerebrovascular reactivity to changes in Pco$_2$ using TCD technology (19,20) have yielded similar results to those obtained with direct measurements of CBF (21,22). If no change in the caliber of the MCA occurs, then changes in MCA flow velocity can be considered proportional to blood flow. However, this remains a potential source of error when extrap-

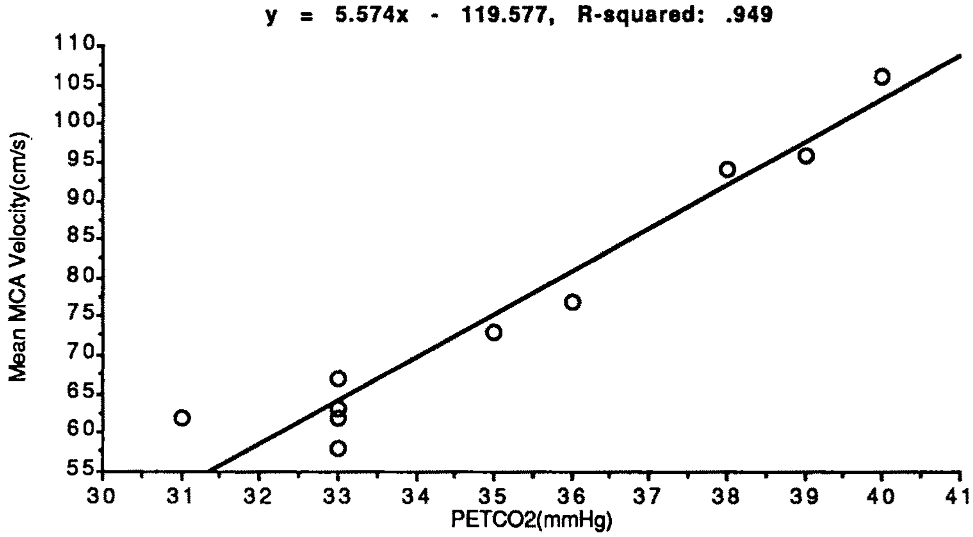

Figure 5. A representative plot of mean MCA flow velocity versus P_{ETCO_2}. A strong positive linear relationship is identified.

olating flow velocity measurements to levels of CBF. Considering the large changes in MCA flow velocity seen in this study, this error is, however, likely to be small. Moreover, should vasodilation of the conductance vessels occur during the study, the error committed would be one of underestimation of the actual increase in CBF and our observations would remain qualitatively valid. Nevertheless, it should be emphasized that because there is considerable variation in the diameter of MCA and therefore in flow velocity between individuals (15), the absolute CBF cannot be estimated from velocity measurements. Within a given individual, however, simultaneous measurements of CBF and MCA flow velocity have demonstrated a good correlation between proportional changes in these two parameters to changing levels of CO_2 (23).

Several other factors may influence the accuracy of the MCA flow velocity measurement. The angle between the ultrasound beam and the course of the vessel under study affects the magnitude of the flow velocity reading, which is a function of the cosine of this angle (15). As the angle between the Doppler signal and flow increases, the apparent MCA flow velocity decreases. The MCA is chosen for flow velocity measurements as the angle of the Doppler signal to flow is small. Moreover, the angle of insonation was fixed using a head harness in this study, thus assuring that any inherent error remained constant within any individual patient so that measurement of changes remained valid. However, this may be a source of error when comparisons are made between patients. Thus, for the calculation of the mean slope of the MCA flow velocity-P_{ETCO_2} plot it was necessary to normalize all data to individual MCA flow velocity at P_{ETCO_2} of 40 mm Hg. Respiratory fluctuations in MCA flow velocity were also evident in some patients, especially at lower P_{ETCO_2} levels. Every attempt was therefore made to measure the MCA flow velocity consistently in the end-expiratory phase averaged over two to three cardiac cycles. Despite these shortcomings, TCD is presently the most ideal or appropriate methodology for a study such as this because the rapid and transient changes in CBF after tourniquet release require instantaneous and continuous measurements that cannot be made with currently available methods for measurement of CBF.

Other changes that occur after tourniquet release, including decreases in Pa_{O_2} and pH and increases in lactic acid, were not measured in this study. Moderate changes in Pa_{O_2} above 100 mm Hg have no significant effect on CBF. With more significant decreases in Pa_{O_2} (to less than 50 mm Hg), CBF increases. Patients in this study were given 40% oxygen in the inspired gas, and arterial oxygen saturation by pulse oximetry was maintained above 96%. Changes in arterial pH of metabolic origin have little effect on CBF. Increased blood levels of lactic acid has, in some animal studies, been shown to increase CBF independently of changes in pH (24). Our results, however, suggest that these metabolic factors probably play a minor role in the increase of CBF after tourniquet release because the slope of the MCA flow velocity-

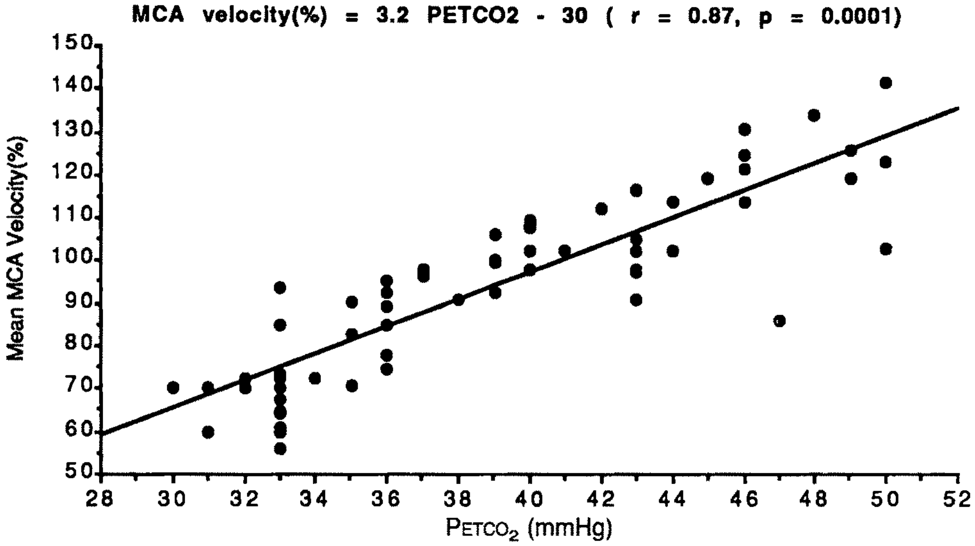

Figure 6. A composite plot of normalized MCA flow velocity versus P_{ETCO_2} using all data collected. Middle cerebral artery velocity was normalized by expressing the absolute velocity as a percentage of the velocity at P_{ETCO_2} of 40 mm Hg determined from individual linear regression analysis. A strong linear relationship is evident, with $r = 0.87$ and $P = 0.0001$. The slope derived is 3.2, indicating that the flow velocity changes by 3.2% per mm Hg change in P_{ETCO_2}.

P_{ETCO_2} regression is essentially the same as two previous studies on CO_2 reactivity using the TCD (19,20). Had these metabolic factors contributed to the increase in CBF, one would anticipate a steeper slope, or at least a higher flow for any given CO_2 during the initial minutes. Such trends were not evident. There are differences between the present study and the two earlier studies (19,20). The subjects in the other two studies were healthy, awake volunteers, whereas our patients were anesthetized. Another difference is the dynamic nature of the changes in P_{ETCO_2} and MCA flow velocity in the present study. Rather than measuring these variables at steady state both were changing over the course of the study. The primary purpose of our study, of course, was not to measure the cerebrovascular-CO_2 response, but to document the change in CBF as reflected by the MCA flow velocity after tourniquet release. These differences notwithstanding, our results are remarkably similar to those of these previous reports.

As demonstrated in Figures 1–4, tourniquet release is followed by an immediate increase in P_{ETCO_2} with a corresponding increase in MCA flow velocity. The mean slope of 3.2% is similar to previously reported values for cerebrovascular-CO_2 response (19,20) and suggests that the increase in MCA flow velocity can be entirely accounted for by the increase in CO_2. Although in most patients both variables returned to near baseline values within 8 min, in two instances the increases in MCA flow velocity and P_{ETCO_2} were sustained for 15 min after tourniquet release. Not surprisingly, in both cases the tourniquet time was relatively long compared with the others (104 and 120 min). Because the magnitude of increase in CO_2 and consequently MCA flow velocity are dependent not only on ischemic time, but also on the metabolic rate and the muscle and tissue bulk rendered ischemic, the relationship between tourniquet time and rise in CO_2 is only a weak one in the present study. The small sample size may also have been a contributing factor.

Despite the strong linear relationship, we observed a difference in the time of maximum increase in P_{ETCO_2} and MCA flow velocity with the latter lagging behind the former by about 2 min (Table 2 and Figures 1 and 2). Several possible explanations for this exist. There could be a time lag in cerebrovascular responses to the change in CO_2. This is, however, unlikely because the time constant of this change has been shown to be quite short (25). Because this was intended to be a noninvasive study, we did not measure Pa_{CO_2}, and it is conceivable that a discrepancy may exist between Pa_{CO_2} and P_{ETCO_2}, one that accounts for these observations. However, Patel et al. (8) studied both variables after tourniquet release in humans and found an identical pattern for Pa_{CO_2} and P_{ETCO_2}, although the Pa_{CO_2} values were slightly higher. The use of P_{ETCO_2} instead of Pa_{CO_2}, therefore, cannot account for the observed difference, nor is the slope that is calculated from P_{ETCO_2} adversely affected, because percentage changes rather than absolute values are used. A more plausible explanation for the lack of correlation between MCA flow velocity and $\mathrm{P_{ETCO_2}}$ peaks lies with the statistically significant decrease in mean blood pressure that occurred over the period between tourniquet release and maximum MCA flow velocity (Figure 3). Harper had previously demonstrated that cerebral vasodilation secondary to hypercapnia can abolish autoregulation and render the cerebral circulation pressure-passive (26). Similar observations on flow velocity have also been made by Aaslid et al. (16). The immediate decrease in mean blood pressure after tourniquet release seen in the present study, accompanied by an increase in $\mathrm{Pco_2}$, may have the effect of reducing the initial rise in MCA flow velocity. Alternatively, vasoactive metabolic products such as lactic acid and potassium released after tourniquet release, although not contributing directly to the increase in CBF, nevertheless rendered the cerebral circulation pressure-passive. A combination of these factors may therefore explain the time-course differences between MCA flow velocity and $\mathrm{P_{ETCO_2}}$.

That $\mathrm{Paco_2}$ levels are a major regulator of cerebrovascular tone, and that a strong correlation existed between MCA flow velocity and $\mathrm{P_{ETCO_2}}$ after tourniquet release support the hypothesis that changes in $\mathrm{P_{ETCO_2}}$ are the major reasons for the increased MCA flow velocity in this study. These observations have important clinical implications. Although the increase in MCA flow velocity and, by inference, CBF is transient in most cases, and well tolerated by otherwise healthy patients, in patients with increased ICP the accompanied increase in cerebral blood volume from vasodilation may be detrimental and may contribute to secondary brain injury, particularly when a long tourniquet time is used. Moreover, this may not be immediately obvious to the attending anesthesiologist because not all patients with suspected decreased intracranial compliance have their ICP monitored. Transcranial Doppler monitoring is noninvasive and would be a viable option in these patients. Or, more simply, because we have demonstrated that this increase in CBF is likely entirely CO_2-mediated, it would be prudent to treat the increase in CO_2 promptly by hyperventilation. Whether a period of hyperventilation immediately before tourniquet release would prevent the increase in CBF remains to be investigated.

The authors thank Drs. Benirschke, Sangeorzan, and Mayo for permission to study their patients, Nancy Sundling for technical and statistical assistance, and Medasonics for supplying the equipment.

References

1. Solonen KA, Tarkkanen L, Narvanen S, Gordin R. Metabolic changes in the upper limb during tourniquet ischaemia. A clinical study. Acta Orthop Scand 1968;39:20–32.
2. Derry R, Pelletier J, Jacques A, et al. Metabolic changes induced in the limb during tourniquet ischaemia. Can Anesth Soc J 1965;12:367–78.
3. Wiligis EF. Observations on the effects of tourniquet ischemia. J Bone Joint Surg 1971;53:1343–6.
4. Benzon HT, Toleikis JR, Meagher LL, Shapiro BA. Changes in venous blood lactate, venous blood gases, and somatosensory evoked potentials after tourniquet application. Anesthesiology 1988;69:677–82.
5. Klenerman L, Biswas M, Hulands GH, Rhodes AM. Systemic and local effects of the application of a tourniquet. J Bone Joint Surg 1980;62B:385–8.
6. Modig J, Kolstad K, Wigre A. Systemic reactions to tourniquet ischaemia. Acta Anaesthesiol Scand 1978;22:609–14.
7. Deen L, Nyst CL, Zuurmond WW. Metabolic changes after tourniquet release. Acta Anaesthesiol Belg 1982;33:107–14.
8. Patel AJ, Choi C, Giuffrida JG. Changes in end tidal CO_2 and arterial blood gas levels after release of tourniquet. South Med J 1987;80:213–6.
9. Lynn AM, Fischer T, Brandford HG, Pendergrass TW. Systemic responses to tourniquet release in children. Anesth Analg 1986;65:865–72.
10. Bourke DL, Silberberg MS, Ortega R, Willock MM. Respiratory responses associated with release of intraoperative tourniquets. Anesth Analg 1989;69:541–4.
11. Valli H, Rosenberg PH. Effects of three anaesthesia methods on haemodynamic responses connected with the use of thigh tourniquet in orthopaedic patients. Acta Anaesthesiol Scand 1985;29:142–7.
12. Conaty KR, Klemm MS. Severe increase of intracranial pressure after deflation of a pneumatic tourniquet. Anesthesiology 1989;71:294–5.
13. Eldridge PR, Williams S. Effect of limb tourniquet on cerebral perfusion pressure in a head-injured patient. Anaesthesia 1989;44:973–4.
14. Aaslid R, ed. Transcranial Doppler sonography. Chapter 4. New York, Wien: Springer-Verlag, 1986:56.
15. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769–74.
16. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;20:45–52.
17. Kontos HA. Validity of cerebral artery blood flow calculations from velocity measurements. Stroke 1989;20:1–3.
18. Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries—angiographic determination in man. Invest Radiol 1967;2:17–32.
19. Markwalder TM, Grolimund P, Seiler RW, Roth F, Aaslid R. Dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure—a transcranial ultrasound Doppler study. J Cereb Blood Flow Metab 1984;4:368–72.
20. Kirkham FJ, Padayachee TS, Parsons S, Seargeant LS, House FR, Gosling RG. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. Ultrasound Med Biol 1986;12:15–21.
21. Grubb B, Mills CD, Colacino JM, Schmidt-Nielsen K. Effects of arterial carbon dioxide on cerebral blood flow in ducks. J Physiol 1977;232:596–608.

22. Olesen J, Paulson OB, Lassen NA. Regional cerebral blood flow in man determined by the initial slope of the clearance of intraarterially injected ^{133}Xe. Stroke 1971;2:519–40.

23. Bishop CCR, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986;17:913–5.

24. Laptook AR, Peterson J, Porter AM. The effects of lactic acid infusions and pH on cerebral blood flow and metabolism. J Cereb Blood Flow Metab 1988;8:193–200.

25. Severinghaus JW, Lassen N. Step hypocapnia to separate arterial from tissue Pco_2 in the regulation of cerebral blood flow. Circ Res 1967;20:272–8.

26. Harper AM. Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. J Neurol Neurosurg Psychiatr 1966;29:398–403.

Comparison of Propofol and Thiopental/Halothane for Short-Duration ENT Surgical Procedures in Children

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BORGEAT A, POPOVIC V, MEIER D, SCHWANDER D. Comparison of propofol and thiopental/halothane for short-duration ENT surgical procedures in children. Anesth Analg 1990;71:511–5.

Experiences with propofol in pediatric anesthesia are limited. We undertook a study to evaluate the quality of induction and recovery from anesthesia with propofol compared to thiopental/halothane. Twenty children received 3 mg·kg^{-1}·min^{-1} of propofol as a loading dose followed by a maintenance dose of 0.1 mg·kg^{-1}·min^{-1} (±10%). Twenty children received 5–7 mg/kg of thiopental, and maintenance was provided with halothane (0.5%–1.5%). The interval between the end of the administration of propofol or thiopental/halothane and extubation, as well to discharge to the ward, was significantly shorter with propofol (4.4 versus 13.5 min and 7.22 versus 30.4 min, respectively). Spontaneous movements and pain on injection were seen significantly more frequently with propofol, whereas laryngospasm and hiccup were only observed with thiopental. During the first 6 h after the surgical procedure, analgesics were needed significantly more often in the thiopental group. Nausea and vomiting also were observed more frequently in the thiopental group. In conclusion, propofol used as a single anesthetic is a satisfactory technique for ENT surgery of short duration in children.

Key Words: ANESTHESIA, PEDIATRIC—propofol, thiopental. ANESTHETICS, INTRAVENOUS—propofol, thiopental.

Propofol is a relatively new intravenous anesthetic (1) for induction and maintenance of anesthesia. It has many advantages, including pharmacokinetic properties contributing to rapid induction and recovery times (2,3). In contrast to studies in adults, there is little experience with propofol in pediatric anesthesia. Therefore we undertook a study to evaluate the quality of induction and recovery from anesthesia with propofol compared to thiopental/halothane in children having ear, nose, or throat (ENT) surgery of short duration.

Patients and Methods

Forty children aged 3–8 yr were studied after hospital ethics committee approval had been obtained. Patients were ASA physical status I and were scheduled for short elective ENT procedures. Exclusion criteria included known allergy to the anesthetic drugs or their constituents, a history of previous adverse experience to general anesthesia, the presence of psychomotor retardation, and general anesthesia with halothane within the last 3 mo.

All patients were premedicated with 0.04 mg/kg oral atropine 60 min before operation. On arrival in the anesthetic room, heart rate and systolic and diastolic blood pressures were recorded using an automatic device (Cardiocap Datex, Helsinki). Other monitors included an electrocardiograph, a pulse oximeter (Cardiocap Datex, Helsinki), a nerve stimulator (Dual Stim, Houston, Tex.), and a precordial stethoscope. A 20- or 22-gauge catheter was inserted into a vein on the dorsum of the hand or in the antecubital fossa.

Children were randomly allocated in an open study to either group A (propofol) or group B (thiopental/halothane). All patients were preoxygenated with 100% oxygen for 1 min. Group A received a loading dose of 3 mg/kg IV propofol immediately followed by a continuous infusion of 0.1 mg·kg^{-1}·min^{-1} (±10%) using an automatic pump (IVAC

Supported in part by ICI Pharmaceutical Division, Lucerne, Switzerland.

Received from the Service d'anesthésiologie-réanimation et d'otorhinolaryngologie, Hôpital Cantonal de Fribourg, CH 1700 Fribourg, Switzerland. Accepted for publication June 24, 1990.

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711, San Diego, Calif.). Group B patients were given 5–7 mg/kg thiopental with maintenance of anesthesia provided by halothane (0.5%–1.5%). Tracheal intubation was facilitated with 0.1 mg/kg IV vecuronium in both groups. A supplemental dose of vecuronium (one-third to one-fourth the initial dose) was given when necessary either as judged by the surgeon or as indicated by reappearance of more than two twitches out of four (nerve stimulator). Anesthetic depth was considered adequate if heart rate and blood pressure were maintained within 20% of preinduction values, with propofol and halothane concentrations adjusted as necessary for pressure and pulse rate to remain within this limit.

Manual ventilation with 33% oxygen and 66% nitrous oxide was used in all patients. Hemoglobin saturation ($\mathrm{Sao_2}$) never decreased below 95%, and the end-tidal carbon dioxide tension ($\mathrm{PECO_2}$) was kept between 35 and 40 mm Hg. At the end of surgery the neuromuscular blockade was reversed with 0.02 mg/kg atropine and 0.04 mg/kg prostigmine. Propofol, halothane, and nitrous oxide were discontinued as soon as the surgeon had terminated the operation (time "0" of the recovery period).

The following conditions had to be fulfilled before extubation: four twitches before reversal of the neuromuscular blockade; spontaneous coordinated movements of the arms; pupils normally dilated and central; spontaneous respiration ($\mathrm{PECO_2}$ less than 45 mm Hg and $\mathrm{Sao_2}$ greater than 95% with 100% oxygen); and opening of the eyes either on command or spontaneously. Stimulation was not permitted except gentle endobuccal suction when necessary.

After extubation the children were transferred to the recovery room, where the awakening was assessed. The following criteria for discharge to the ward had to be fulfilled: the child had to be awake and alert, able to sit unaided, and able to communicate according to age and to execute simple orders.

The recovery room nurses were responsible for the transfer of the children to the ward (according to the discharge criteria) and were not informed of the anesthetic drugs used. Neither opiates nor benzodiazepines were given either as premedication or during surgery.

Statistical analysis of the results was carried out using a nonparametric approach with the Mann–Whitney test and χ^2 with Yates' correction for small numbers when appropriate. Student's *t*-test was used to compare demographic data. Results are given as mean ± SEM. $P < 0.05$ was considered as significant.

Table 1. Characteristics of Patients

	Propofol group	Thiopental/halothane group
n	20	20
Age (yr)	6.09 ± 1.64 (3–8)	5.11 ± 2.26 (3–8)
Weight (kg)	20.5 ± 9.07 (16–32)	21.5 ± 5.96 (14.8–30)
Sex (M/F)	9/11	8/12
Operating time (min)	37 ± 12.1	34.9 ± 11.35
Type of surgery		
Adenoidectomy	6	5
Tonsillectomy	7	8
Adenoidectomy and tonsillectomy	5	7
Other	2	

Values for age, weight, and operating time are mean ± SD. Ranges are given in parentheses.

Table 2. Interval Between End of Drug Administration and Extubation and Discharge From the Recovery Room

	Propofol group	Thiopental/halothane group
Time to extubation (min)	4.4 ± 0.74	13.5 ± 2.32
Time to discharge from recovery room (min)	7.22 ± 0.59	30.4 ± 4.03

Values are mean ± SEM.

Results

The ages, weights, sex, duration, and type of surgical procedures were similar in both groups (Table 1). There were 23 girls and 17 boys.

The interval between the end of the administration of propofol or halothane and extubation was significantly shorter in group A (propofol): 4.4 ± 0.74 min versus 13.5 ± 2.30 min ($P < 0.005$) in group B (halothane) (Table 2). In group A, all patients fulfilled the extubation criteria, whereas in group B 16 of the 20 patients (80%) did not open their eyes before extubation. However, extubation had to be performed because of coughing and struggling due to the presence of the endotracheal tube.

The time between the end of the administration of propofol or halothane and the completion of the criteria for discharge from the recovery room was also significantly shorter with propofol (7.22 ± 0.59 min) than with thiopental/halothane (30.4 ± 4.03 min) ($P < 0.005$) (Table 2).

During induction in the propofol group, mean arterial pressure decreased 11.2% after 1 min to a maximum of 14.3% after 2 min. Heart rate remained stable or showed a slight decrease of 5%–10% of preinduction values. In the thiopental group mean

Table 3. Incidence of Side Effects During Induction

Side effect	Propofol group	Thiopental/halothane group
Pain	5 (25%)	—
Spontaneous movements	15 (75%)	4 (20%)
Laryngospasm	—	1 (5%)
Hiccup	—	1 (5%)

Table 4. Quality of Awakening

Activity	Propofol group	Thiopental/halothane group
Agitated, uncooperative, crying	1 (5%)	14 (70%)
Nausea, emesis	—	2 (10%)
Need for analgesic	1 (5%)	9 (45%)

arterial pressure decreased by 13.5% after 1 min to a maximum of 15% after 90 s, whereas heart rate showed a slight increase of 8%–12% of preinduction values. During maintenance of anesthesia in both groups, heart rate and blood pressure remained stable and were easily adjusted by slight increase or decrease of perfusion rate of propofol or percentage of halothane.

Side effects during induction are summarized in Table 3. In group B pain was not experienced. In group A the incidence of pain on injection was 25%. Four of the children who had pain on injection had a 22-gauge catheter inserted in the dorsum of the hand; one had a 22-gauge catheter in a small vein in the antecubital fossa. Spontaneous movements occurred during induction in 75% of children receiving propofol and in 20% receiving thiopental. Laryngospasm and hiccup occurred in one child in group B (halothane).

Quality of recovery was excellent in all children in group A, except for one who cried, whereas 70% of the patients in group B were described as agitated, uncooperative, and crying. During the first six postoperative hours analgesics were needed in one child in group A (5%) and in nine (45%) in group B. Nausea and emesis were absent in group A but occurred in two children (10%) in group B (Table 4).

All children in the propofol group were able to recall within 4 min of extubation the picture of a familiar animal (cat, dog) shown to them before induction.

Discussion

Recovery after propofol, one of the striking features of this drug, has been commented on by many investigators: rapid emergence and minimal postoperative confusion are characteristic (4–7). However, the vast majority of studies of recovery from propofol have been carried out in adults.

The present study shows that the quality of recovery in children after short-duration ENT surgery using propofol as a principal agent is very satisfactory. The intervals between cessation of drug administration and both extubation and transfer from the recovery room to the ward were significantly shorter with propofol than with thiopental/halothane: 4.47 versus 13.5 min and 7.22 versus 30.4 min, respectively. In adults undergoing relatively brief operations, the mean interval between cessation of propofol and extubation was 11 min (8); however, these patients were premedicated with oral diazepam (10 mg), and the first-stage elimination half-life ($t_{1/2\beta}$) of propofol is shorter in children (9). Using criteria similar to ours (pediatric outpatient dental anesthesia), Puttick and Rosen (10) found a mean recovery time of 22 min with propofol and 29 min with thiopental/halothane, findings similar to ours. The shorter recovery time found in our study could be explained in part by the advantage of a continuous infusion compared with a supplemental bolus administration technique. Indeed, continuous intravenous infusion showed little accumulation, and thus clinical effects are predictable, e.g., consistently rapid recovery (11,12). All children, except the one who cried, were quiet, well oriented and coordinated, and cooperative in the recovery room, whereas 70% of patients in the thiopental/halothane group were crying, agitated, uncoordinated, and uncooperative during the first 20 min.

Previous studies have demonstrated that children may need larger induction doses of propofol than adults (13,14). Purcell-Jones and James (15) showed that a dose of 2.0 mg/kg in premedicated children was not always sufficient for a smooth induction. Also, Valtonen et al. (14) were not entirely satisfied with a loading dose of 2.0–2.5 mg/kg in premedicated children. Because premedication has little effect on the smoothness of induction (16), we chose a dose of 3 mg/kg for this study. Even though atropine was the only drug used for premedication, only four children exhibited signs of anxiety and fear before induction.

The incidence of pain on injection in adults has been reduced by the use of a fat emulsion as a vehicle for propofol (17). We found a 25% incidence of pain with propofol and none with thiopental. These results are similar to those of Purcell-Jones et al. (24% for propofol and 10% for thiopental) (13). The incidence of pain on injection in adults is higher when the smaller veins on the dorsum of the hand are used

(18,19). Children had a 30% incidence of pain according to Saint-Maurice et al. (20). In their study, pain was associated with the size of the vein used, which we also noted. All five children who experienced pain on injection had a 22-gauge catheter (the smallest size used in this study). The catheter was inserted in four cases in the dorsum of the hand and in the fifth case in a small vein of the antecubital fossa. Addition of lidocaine to propofol decreases pain on injection (9,10), but the role of premedication, including use of analgesics, is not yet clear.

Spontaneous movements have been reported in 14%–33% (21,22) of adults. Our observation of 75% is greater than that reported by Fahy et al. in premedicated adults (22) and Purcell-Jones et al. (33%) (13), but similar to the 65% incidence observed by Purcell-Jones and James (15); however, in the latter study the loading dose of propofol was small (2 mg/kg). All of these movements, however, were minor in our study, appearing a few seconds after the completion of injection and lasting no longer than 25 s. Saint-Maurice et al. (20) suggest a possible inadequate anesthesia when using a loading dose of 2–2.5 mg/kg of propofol. The influence of premedication and the speed of injection on the incidence of spontaneous movements is not clear; further studies are needed to evaluate whether inadequate anesthesia and central or peripheral stimulation are involved in the genesis of spontaneous movements during induction with propofol. The number of patients with spontaneous motion is smaller (20%) in the thiopental group, as previously reported (13,14). Hiccup and laryngospasm were observed in two children receiving thiopental and in none given propofol; this tendency is also similar to published data (14).

Side effects such as pain or nausea and emesis were less frequent during the first postoperative hours in the propofol group. This was also reported by McCollum and colleagues (23), who found less nausea and vomiting after induction with propofol than after induction with methohexital. Briggs and colleagues (24) suggested that propofol produces some analgesic effect, contrary to the antianalgesic effect of thiopental; it is interesting that in the present study only one child needed an analgesic postoperatively in the propofol group whereas nine children in the thiopental/halothane group needed an analgesic.

In conclusion, previous studies dealing with children have stressed induction characteristics (9,15), combined use of propofol and inhaled anesthetics (13,14,20), or propofol given by bolus (10). The present study shows that continuous perfusion of propofol is a safe and more effective anesthetic technique than the usual thiopental/halothane combination for short-duration ENT procedures in children. The rapidity and quality of awakening after propofol is superior to that observed after thiopental/halothane administration. The incidence of spontaneous movements and pain on injection is greater with propofol than with thiopental. On the other hand, excitatory side effects such as hiccup or laryngospasm were more frequently observed in the thiopental group. Further studies are needed to find a means of reducing the pain on injection associated with propofol and to understand more completely the process of spontaneous movements associated with the use of propofol for induction in children.

The authors thank James Grainger for his help in the preparation of the manuscript.

References

1. Kay B, Rolly C. I.C.I. 35868, a new intravenous induction agent. Acta Anaesthesiol Belg 1977;28:303–16.
2. Nightingale P, Healy TES, Hargreaves J, McGuiness K, Kay B. Propofol in emulsion form: induction characteristics and venous sequelae. Eur J Anaesthesiol 1985;2:361–8.
3. Cockshott ID. Propofol pharmacokinetics and metabolism—an overview. Postgrad Med 1985;61(Suppl 3):45–50.
4. Mackenzie N, Grant, IS. Comparison of propofol with methohexitone in the provision of anaesthesia for surgery under regional blockade. Br J Anaesth 1985;57:1167–72.
5. Johnston R, Noseworthy T, Anderson B, Konopad E, Grace M. Propofol versus thiopental for outpatient anesthesia. Anesthesiology 1987;67:431–3.
6. Mackenzie N, Grant IS. Propofol ("Diprivan") for continuous intravenous anesthesia. A comparison with methohexitone. Postgrad Med J 1987;61(Suppl):70–5.
7. Grant IS, Mackenzie N. Recovery following propofol ("Diprivan") anesthesia—a review of three different anaesthetic techniques. Postgrad Med J 1985;61(Suppl):133–7.
8. Queruel PL, Francon D, Lacorelle B, François G. Le réveil après anesthésie au propofol pour chirurgie ORL de courte durée. Ann Fr Anesth Reanim 1987;273–6.
9. Valtonen M, Iisalo E, Kanto J, Rosenberg P. Propofol as an induction agent in children: pain on injection and pharmacokinetics. Acta Anaesthesiol Scand 1989;33:152–5.
10. Puttick N, Rosen M. Propofol induction and maintenance with nitrous oxide in paediatric outpatient dental anaesthesia. A comparison with thiopental-nitrous oxide-halothane. Anaesthesia 1988;43:646–9.
11. Jessop E, Grounds RM, Morgan M, Lumley L. Comparison of infusions of propofol and methohexitone to provide light general anesthesia during surgery with regional block. Br J Anaesth 1985;57:1173–7.
12. Kay B, Hargreaves J, Sivalingam T, Healy TEJ. Intravenous anesthesia for cystoscopy: a comparison of propofol or methohexitone with alfentanil. Eur J Anaesthesiol 1986;3:111–20.
13. Purcell-Jones G, Yates A, Baker JR, James IG. Comparison of the induction characteristics of thiopentone and propofol in children. Br J Anaesth 1987;59:1431–6.

14. Valtonen M, Iisalo E, Kanto J, Tikkanen J. Comparison of propofol and thiopentone for induction of anaesthesia in children. Anaesthesia 1988;43:696–9.
15. Purcell-Jones G, James IG. The characteristics of propofol ("Diprivan") for the induction of general anesthesia for paediatric surgery. Postgrad Med J 1985;61(Suppl 3):115.
16. Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35 868. Br J Anaesth 1984;56:617–25.
17. Cummings GC, Spence AA. Comparison of propofol in emulsion with althesin for induction of anesthesia. Br J Anaesth 1985;57:234–5.
18. Kawar P, Dundee JW. Frequency of pain on injection and venous sequelae following the IV administration of certain anaesthetics and sedatives. Br J Anaesth 1982;54:935–9.
19. Mackenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for inducing anaesthesia in day-cases. Br J Anaesth 1985;57:725–31.
20. Saint-Maurice C, Landais A, Cockshott ID, et al. Le propofol comme agent d'induction en anesthésie pédiatrique: étude clinique préliminaire. Ann Fr Anesth Reanim 1987;6:269–72.
21. Stark RD, Binks SM, Dutka VN, O'Connor KM, Arnstein MJA, Glen JB. A review of the safety and tolerance of propofol. Postgrad Med J 1985;61:152–6.
22. Fahy LT, Van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol. Anaesthesia 1985;40:939–44.
23. McCollum JS, Milligan KR, Dundee JW. The antiemetic action of propofol. Anaesthesia 1988;43:239–40.
24. Briggs LP, Dundee JW, Bahar M, Clarke RSS. Comparison of the effect of diisopropyl phenol (ICI 35868) and thiopentone on response to somatic pain. Br J Anaesth 1982;54:307–11.

Preoxygenation in the Elderly: A Comparison of the Four-Maximal-Breath and Three-Minute Techniques

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VALENTINE SJ, MARJOT R, MONK CR. Preoxygenation in the elderly: a comparison of the four-maximal-breath and three-minute techniques. Anesth Analg 1990;71:516–9.

To compare the effectiveness of two routinely used methods of preoxygenation in protecting against hypoxia in the elderly, the arterial O_2 saturation was measured using an oximeter. Twenty-four elderly patients (≥65 yr) presenting for elective orthopedic surgery were randomly allocated to receive either 3-min or four-maximal-breaths of 100% O_2 via a Bain circuit. After preoxygenation, anesthesia was induced, tracheal intubation performed with patients kept apneic, and the endotracheal tube left open to air. The arterial O_2 saturation was measured before preoxygenation and continually recorded during desaturation. Although attaining similar arterial O_2 saturation values after preoxygenation, patients in the four-maximal-breath group had significantly shorter times ($P < 0.0001$) to all levels of desaturation. We suggest that preoxygenation with 3-min breathing of 100% O_2 offers more protection against hypoxia due to prolonged apnea after induction of anesthesia in the elderly than does four maximal breaths of 100% O_2.

Key Words: OXYGEN, DENITROGENATION, preinduction. INDUCTION, ANESTHESIA—preoxygenation.

Preoxygenation is recommended before the induction of anesthesia and muscle paralysis, particularly if there is increased risk of gastric regurgitation or if a difficult intubation is expected. The preoxygenation with 100% oxygen (O_2) replaces the nitrogen contained in the functional residual capacity and so prolongs the time before hypoxia occurs after the onset of apnea. Previous studies have compared the different methods of preoxygenation but mainly in younger ASA physical status I and II patients (1–5). The question of the relative efficacies of a four-maximal-breath and a 3-min technique has not been addressed in an elderly population, and yet it has important connotations for both routine and emergency geriatric anesthesia where both methods are accepted practice.

Patients and Methods

The study was approved by the hospital ethical committee, and written informed consent was obtained from all patients. Twenty-four elderly patients (aged ≥65 yr) presenting for routine orthopedic surgery were prospectively studied after being randomly allocated to receive either the 3-min or four-maximal-breath technique of preoxygenation. Patients excluded were those with clinically significant cardiovascular, respiratory, neurologic, or endocrine disease, as were patients with obesity or those in whom difficult intubation could be predicted. During the preoperative assessment, the appropriate method of preoxygenation was explained to each patient. Premedication was with oral tempazepam (0.1–0.2 mg/kg) given 90 min preoperatively.

In the anesthetic room the patients were again instructed in the technique of preoxygenation, and intravenous access was secured with a 16-gauge cannula. Monitoring was with a Dinamap (1846SX) automated blood pressure device, electrocardiogram in the CM5 configuration, and a pulse oximeter (Datex Satlite) applied to a thumb. Baseline measurements were recorded with patients breathing air. Patients were pretreated with atropine (10 μg/kg) and vecuronium (10 μg/kg) 3 min before induction.

Preoxygenation was accomplished with an appropriately sized face mask connected to a Bain circuit that had been flushed with 100% O_2. The O_2 flow rate was 10 L/min in the 3-min group and 35 L/min in the four-maximal-breath group to maintain the filling of the reservoir bag during inspiration and prevent any

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Received from the Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Marlborough Street, Bristol, United Kingdom. Accepted for publication July 2, 1990.

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Table 1. Demographic Data and Times to Apnea

Group	Age (yr)	Height (m)	Weight (kg)	Sex (M/F)	Hb (g/dL)	Time to apnea (s)
4 VC[a]	74.6 ± 6.0	1.71 ± 0.09	63.4 ± 8.8	9/3	14.4 ± 1.2	40.4 ± 5.0
(n = 12)	(62–73)	(1.57–1.88)	(51–74)		(12.6–16.8)	(30–45)
3 min[b]	79.2 ± 5.9	1.65 ± 0.07	62.8 ± 8.1	9/3	14.3 ± 1.3	39.2 ± 9.5
(n = 12)	(70–92)	(1.55–1.78)	(53–74)		(11.8–16.7)	(20–50)

Hb, hemoglobin.

Values are mean ± SD, with range given in parentheses.

[a] Patients receiving the four-vital-capacity-breath method of preoxygenation.

[b] Patients receiving the 3-min method of preoxygenation.

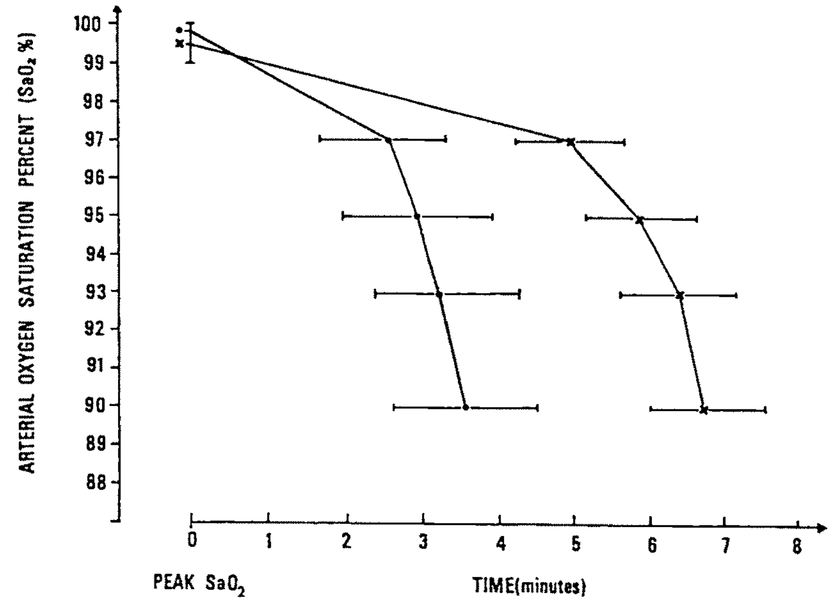

Figure 1. Times to decrease in saturation from peak Sao_2 to lowest Sao_2 levels. ●, four-maximal-breath group; X, 3-min group.

rebreathing. Patients in the 3-min group were asked to continue to breathe normally after application of the face mask while preoxygenation was performed for 3 min. Patients in the four-breath group were asked to exhale maximally, an effective seal being obtained with the face mask, and then requested to take four maximal breaths. They were then told to breathe normally.

Immediately after completing the preoxygenation maneuvers anesthesia was induced with thiopental (2–4 mg/kg) and succinylcholine (1.5 mg/kg). The patients were not ventilated until the end of the study. With the onset of anesthesia and muscle paralysis cricoid pressure was applied, and the patients' trachea intubated under direct vision. After successful intubation was visually confirmed the endotracheal tube was left open to air. If visual confirmation was not possible the patient was excluded from the trial, the airway secured, and the lungs ventilated with 100% O_2. Supplemental doses of thiopental (1 mg/kg) and succinylcholine (0.5 mg/kg) were given every 2 min to maintain anesthesia and muscle paralysis. A continuous recording of the arterial O_2 saturation (Sao_2) was made and the heart rate and blood pressure recorded at 1-min intervals. The study was completed when the Sao_2 had decreased to 90%, the lungs then being ventilated with 100% O_2 until the Sao_2 was greater than 97%.

The demographic data were compared by analysis of variance. Arterial O_2 saturation while breathing air, the peak Sao_2 obtained after preoxygenation, and mean times to the onset of apnea and each desaturation point were compared using the Mann–Whitney U test. P values of less than 0.05 were considered to be statistically significant.

Results

The demographic data for the two groups are shown in Table 1. There is no significant difference in age, height, weight, hemoglobin concentration, or time to apnea after induction of anesthesia. The number of men and women was similar in each group, with a similar distribution of smokers and nonsmokers. No

Table 2. Oxygen Saturation Levels Before and After Preoxygenation and Times to Arterial Desaturation

Group	Sa_{O_2} on air	Peak Sa_{O_2} on 100% O_2	Time to 97% Sa_{O_2}	Time to 95% Sa_{O_2}	Time to 93% Sa_{O_2}	Time to 90% Sa_{O_2}
4 VC[a]	95.4 ± 1.7	99.8 ± 0.5	147.5 ± 82.4	177.1 ± 90.7	193.7 ± 92.1	212.1 ± 91.8
(*n* = 12)	(93–97)	(99–100)	(30–260)[c]	(50–310)[c]	(70–315)[c]	(80–320)[c]
3 min[b]	95.2 ± 2.2	99.5 ± 0.8	296.7 ± 72.5	315.3 ± 69.5	382.9 ± 74.2	405.8 ± 75.4
(*n* = 12)	(92–98)	(98–100)	(220–450)	(265–500)	(275–530)	(290–550)

Sa_{O_2}, arterial oxygen saturation.
Values are mean ± SD, with the range given in parentheses.
Time is given in seconds.
[a] Patients receiving the four-vital-capacity-breath method of preoxygenation.
[b] Patients receiving the 3-min method of preoxygenation.
[c] $P < 0.0001$.

significant hemodynamic disturbance occurred in any patient, and all patients were successfully intubated at the first attempt. After completion of the study and hand ventilation with 100% O_2, Sa_{O_2} values in all patients were 97% or greater within 45 s. No patient recalled any events after induction.

The saturation results are shown in Table 2 and Figure 1. There was no significant difference between the two groups in Sa_{O_2} while breathing air, or in the peak Sa_{O_2} after preoxygenation. Patients in the four-maximal-breath group had significantly shorter times to desaturation to each Sa_{O_2} level recorded ($P < 0.0001$). The times to 90% saturation were 212.1 + 91.8 s in the four-breath group and 405.8 + 75.4 s in the 3-min group. Four patients in the maximal-breath group desaturated to 90% in 2 min or less. The shortest time to this level of desaturation in the 3-min group was 4 min 50 s.

Discussion

Various methods of preoxygenation to protect against hypoxemia after induction of anesthesia have been recommended. Previous studies of these techniques have been primarily restricted to fit young adult patients or volunteers (1–5). This study has examined the efficacy of two standard techniques of preoxygenation in an elderly population scheduled for elective surgery. The design of the study ensured airway protection allowing for rapid oxygenation once the saturation had decreased to 90% or if any deterioration in patient condition occurred. By leaving the endotracheal tube open to air and keeping the patient anesthetized and apneic, the O_2 reserve was measured by observation of the time required for arterial desaturation to occur after induction of anesthesia. Other investigators have estimated O_2 reserve indirectly by measuring arterial O_2 tension (Pa_{O_2}) (2), but factors other than Pa_{O_2} at completion of preoxygenation may influence O_2 reserve (3).

Drummond and Park have shown that age, forced expiratory volume, forced vital capacity, and smoking habits were not related to the rapidity of desaturation after induction of anesthesia, but that obesity was (1). They suggested that three vital capacity breaths of 100% O_2 would allow a 3-min period of apnea before the onset of hypoxemia. Without preoxygenation, only 1 min elapsed before significant desaturation occurred. Gold and Muraavchick compared four maximally deep breaths of 100% O_2 against air in patients (aged 40–73 yr), and found Pa_{O_2} values higher in the preoxygenation group at the time of intubation (2). No comment was made on the effect of age on Pa_{O_2}. In comparing four maximal breaths with 3 min of preoxygenation in ASA physical status I patients (aged 23–37 yr) Gambee et al. reported that although the Sa_{O_2} remained above 90% for more than 4 min of apnea in both groups, the latter technique gave longer protection against desaturation (3).

Norris and Dewan (5) showed that in the pregnant patient there was no difference in the Pa_{O_2} in maternal or fetal samples after 3 min or four maximal breaths of preoxygenation. These studies suggest that the four-maximal-breath technique affords adequate protection against inadvertent desaturation. Our investigation was designed to test the efficacy of this technique in geriatric patients presenting for elective orthopedic surgery.

There were no demographic differences between the two groups of patients in our study, and times to apnea were the same, implying that the period of breathing 100% O_2 was similar in the two groups after induction of anesthesia but before onset of muscle paralysis. Patients in our four-maximal-breath group were told to breathe normally after their last maximal breath, thus avoiding the possibility of active exhalation and loss of the expiratory reserve volume immediately before apnea. The patients assigned to the four-maximal-breath technique had two rehearsals of the procedure preoperatively (once in the ward and once in the anesthetic room), and all cooperated to the best of their ability. This rehearsal and cooperation might not be possible with some geriatric patients.

We found in our elderly patients similar Sao_2 values before and after preoxygenation with these two techniques. However, there was a significantly shorter time to all levels of desaturation associated with the four-maximal-breath method. Four patients in this group desaturated to 90% in 2 min or less. The shortest time to 90% saturation in the 3-min group was 4 min 50 s. This difference between our two groups is presumably due to physiologic changes in the respiratory system of the elderly. The aging process is associated with parenchymal changes of the diffuse emphysematous type within the lungs, changes that decrease the alveolar surface area (6,7). The reduced total elastic recoil of the lungs impairs the function of the distal airways with airway closure occurring at the higher lung volumes (8). This encroachment of the closing volume into the tidal volume creates ventilation-perfusion mismatch. The respiratory muscles (diaphragm and intercostal and accessory muscles) act on a less compliant chest wall and are themselves weaker, with decreased strength and speed of contraction (9–11). The vital capacity and inspiratory and expiratory reserve volumes are all diminished. These effects combine to reduce the pulmonary reserve of the elderly in general and appear in particular to render the four-maximal-breath technique less effective in denitrogenating the functional residual capacity.

In summary, we found that in this study of elective geriatric patients the four-maximal-breath technique gives similar peak Sao_2 values to the 3-min technique after preoxygenation. However, it does not give reliable protection against desaturation during apnea. We therefore suggest that if preoxygenation is to be performed in the elderly, the 3-min technique should be used.

References

1. Drummond GB, Park GR. Arterial oxygen saturation before intubation of the trachea: an assessment of oxygenation techniques. Br J Anaesth 1984;56:987–92.
2. Gold MI, Muraavchick S. Arterial oxygenation in conscious patients after 3 minutes and after 30 seconds of oxygen breathing. Anesth Analg 1981;60:313–5.
3. Gambee AM, Hertzka RE, Fisher DM. Preoxygenation techniques: comparison of three-minutes and four-breaths. Anesth Analg 1987;66:468–70.
4. Berthoud M, Read DH, Norman J. Preoxygenation—how long? Anaesthesia 1983;38:96–102.
5. Norris MC, Dewan MD. Preoxygenation for cesarian section: a comparison of two techniques. Anaesthesiology 1985;62:827–9.
6. Azcuy A, Anderson AE Jr, Foraker AG. The morphological spectrum of aging and emphysematous lungs. Ann Intern Med 1962;57:1–17.
7. Pump KK. The aged lung. Chest 1971;60:571–7.
8. Stephen CR, Assaf RAE. Geriatric anaesthesia: principles and practice. London: Butterworth, 1986:69.
9. Mittman C, Edelman NH, Norris AH. Relationship between chest wall and pulmonary compliance and age. J Appl Physiol 1965;20:1211–6.
10. Robinson S. Physical fitness in relation to age. In: Cander L, Moyer JH, eds. Ageing of the lung: perspectives. New York: Grune & Stratton, 1964:287–301.
11. Du Bois AB, Alaela R. Airway resistance and mechanics of breathing in normal subjects 75 to 90 years of age. In: Cander L, Moyer JH, eds. Ageing of the lung: perspectives. New York: Grune & Stratton, 1964:156–62.

ANESTH ANALG
1990;71:520–8

Cardioprotective Effects of Carnitine in Extensive Aortocoronary Bypass Grafting:

A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

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DEMEYERE R, LORMANS P, WEIDLER B, MINTEN J, VAN AKEN H, FLAMENG W. Cardioprotective effects of carnitine in extensive aortocoronary bypass grafting: a double-blind, randomized, placebo-controlled clinical trial. Anesth Analg 1990;71:520–8.

The cardioprotective effects of carnitine were tested in patients undergoing multiple aortocoronary bypass grafting. Intermittent aortic cross-clamping at 28°C was used. Mean total cross-clamping time was 30 ± 11 min. Patients were randomized into three groups: a control group receiving placebo (group 1), a group pretreated with 3 g carnitine intravenously before cardiopulmonary bypass (CPB) (group 2), and a group pretreated with 6 g carnitine intravenously (group 3). The markers of myocardial ischemia included levels of adenosine triphosphate, its catabolites, and creatine phosphate in transmural left ventricular biopsy specimens taken at the beginning and end of CPB, as well as hemodynamic recovery during weaning from CPB and for the next 24 h. The intravenous infusion of carnitine (3 or 6 g) had no hemodynamic effect. At the end of CPB myocardial tissue levels of adenosine triphosphate and creatine phosphate did not differ significantly among the groups ($P > 0.05$). Recovery of cardiac function during weaning from CPB and for the following 24 h was similar in all three groups ($P > 0.05$). It is concluded that pretreatment with carnitine neither facilitates weaning from cardiopulmonary bypass in patients undergoing aortocoronary bypass surgery nor favorably affects hemodynamic function during the next 24 h.

Key Words: ANESTHESIA, CARDIOVASCULAR—carnitine protection. SURGERY, CARDIOVASCULAR—carnitine protection.

Carnitine (3-hydroxy-4*N*-trimethyl-aminobutyrate) is the requisite carrier for mitochondrial transmembrane movements of long-chain fatty acids (1,2). During ischemia, the acyl coenzyme A (CoA) content of the myocardium is increased (3,4). Shug et al. (4) and Shrago et al. (5) have shown that accumulation of acyl CoA can be linked to impaired adenine translocase activity in the ischemic heart. Consequently, impaired mitochondrial energy production during myocardial utilization of fatty acids might be an important cause of myocardial damage during ischemia (6). Also, carnitine can reverse long-chain acyl CoA inhibition of mitochondrial adenine nucleotide translocase in isolated mitochondrial preparations (7). Furthermore, carnitine has been reported as having a protective effect in ischemic dog (8) and swine myocardial tissues (9), and as preventing serious arrhythmias in ischemic swine (10) and cat hearts (11). Finally, Thomsen et al. (12) have demonstrated an improved pacing tolerance of the ischemic human myocardium after administration of carnitine.

To determine if the above reports might reflect potential benefits in patients, we studied the effect of carnitine pretreatment on ischemia tolerance of the human heart in patients undergoing aortocoronary bypass grafting. As indices of myocardial protection we evaluated the myocardial tissue content of adenosine triphosphate (ATP), its metabolites, and creatine phosphate (CrP) in biopsy specimens taken from the left ventricle before and after global ischemia, as well as the recovery of hemodynamic function during the first 24 h after weaning from cardiopulmonary bypass (CPB).

Received from the Departments of Anesthesiology, Katholieke Universiteit, Leuven, Belgium, and from Fresenius AG, Bad Homburg, Germany. Accepted for publication July 9, 1990.

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Materials and Methods

Sixty patients scheduled for elective aortocoronary bypass grafting were included in a double-blind, placebo-controlled, randomized study. Criteria for inclusion were as follows: coronary artery disease necessitating elective aortocoronary bypass grafting, no evidence of acute myocardial infarction, and no associated cardiac disease, including left ventricular aneurysm. Patients had to have recurrent angina pectoris. Preoperative data were collected, including age, sex, body surface area, diagnosis, accompanying diseases, patient's history, and medications.

The 60 patients were randomly assigned to three groups of 20 patients each. In group 1 intermittent aortic cross-clamping at 28°C was preceded by the intravenous (IV) injection of placebo before the start of CPB over a 10-min period. In group 2 intermittent aortic cross-clamping at 28°C was preceded by the IV infusion of 3 g carnitine over a 10-min period before CPB. In group 3 intermittent aortic cross-clamping at 28°C was preceded by the IV infusion of 6 g carnitine over a 10-min period before the start of CPB. The study was performed with the permission of the institution's Human Studies Committee as well as with the informed consent of the patients.

Anesthetic management was standardized. Premedication consisted of sublingual lorazepam (0.06 mg/kg) before induction. Upon arrival in the operating theater, an electrocardiograph was attached and a V_5 lead continuously displayed. Cannulae were inserted into a peripheral vein and a radial artery using local anesthesia. A continuous infusion of lactated Ringer's solution was started. Anesthesia was induced with 3–4 μg/kg sufentanil and 3 mg/kg thiopental, followed by 0.1 mg/kg pancuronium bromide. All patients continued to breath 100% oxygen spontaneously by face mask and, upon disappearance of the eyelash reflex, were manually ventilated. Four minutes after induction, tracheal tubes were inserted, and mechanical ventilation with an air-oxygen mixture (F_{IO_2}, 0.5) was started and adjusted to maintain an arterial Pa_{CO_2} of 38–43 mm Hg and an end-tidal carbon dioxide level of 4.5%–5%. Anesthesia was maintained with sufentanil.

A balloon-tipped flow-directed thermodilution catheter was inserted into the pulmonary artery via the internal jugular vein. All pressures were recorded using Statham transducers and continuously displayed on a six-channel chart recorder.

Lactated Ringer's solution and a hydroxyethylstarch solution were administered intravenously to maintain a pulmonary capillary wedge pressure of 8 mm Hg.

Lidoflazine (1 mg/kg) was slowly infused intravenously over at least 10 min, starting 30 min before CPB (13).

After 300 IU/kg heparin had been given and aortic cannulation performed, a 7-F Millar microtip manometer was placed into the left ventricle (LV) via the right pulmonary vein for monitoring of left ventricular pressure and its first derivative, LV dP/dt. After a period of stabilization, a placebo, 3 g carnitine, or 6 g carnitine was administered intravenously over 10 min according to the randomization schema.

Hemodynamic parameters (listed below) were measured before, every minute during, and 10 min after drug or placebo administration, and 1, 5, 10, and 15 min after cessation of CPB. With the exception of left ventricular contractility, the same parameters were also measured 1, 6, 12, 18, and 24 h after cessation of CPB. The hemodynamic parameters measured included heart rate, systemic systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, and central venous pressure. Cardiac output (Cardiac Output Computer 9510, American Edwards Laboratories, Irvine, Calif.) was measured by the thermodilution technique using iced glucose solution. The average of three measurements of cardiac output was used to determine cardiac output. Left ventricular contractility was estimated by the first derivative of the left ventricular pressure (LV dP/dt_{max}). Systemic vascular resistance, cardiac index, stroke index, left ventricular stroke work index, and right ventricular stroke work index were calculated using standard formulas (14).

Before the start of CPB, a second dose of 0.1 mg/kg pancuronium was given.

During CPB, the lungs were not ventilated and were allowed to remain collapsed with a static inflation pressure of 5 mm Hg. Cardiopulmonary bypass was conducted with a membrane oxygenator (Maxima-Metronic) and Sarns roller pumps. Immediately after the onset of CPB, a left ventricular transmural biopsy specimen was taken (Tru-Cut-Travenol biopsy needle) from the anterior free wall approximately 5 cm above the apex. Thereafter the patient was cooled to 28°C. Next, the heart was vented via a cannula inserted into the LV via the right pulmonary vein after removal of the tip manometer. Intermittent aortic cross-clamping was used to perform the distal anastomosis. After rewarming to 35°C rectal temperature, but before cessation of CPB, another biopsy specimen was taken from the same area.

Before weaning from CPB, ventilation was started again with an oxygen-air mixture (F_{IO_2} 0.5). At the end of CPB, the blood in the oxygenator or fresh blood was slowly transfused until a ventricle filling pressure (left atrial pressure) of 8 mm Hg was attained. No patient was given a positive inotropic compound or a vasodilator during the first few minutes after cessation of CPB so that immediate postbypass cardiac performance could be evaluated. The aortic cannula was kept in place for 5 min after cessation of CPB. If the hemodynamic status remained stable, cannulae were removed between minute 5 and minute 10 to 15. After 15 min, protamine hydrochloride was given to neutralize the heparin.

Biochemical Analysis

Transmural left ventricular biopsy specimens were immediately (within 3 s) cooled in liquid nitrogen and stored at −80°C. Adenosine triphosphate and CrP levels were determined by luminometry (Luminometer 1250, ATP bioluminescence kit CLS, Boeringer, F.R.G.). Nucleotides and nucleosides were separated by high-performance liquid chromatography in one single run using a reversed-phase C-18 column (14). Tissue contents were calculated as millimoles per milligram of dry weight. Blood samples were obtained shortly before and at 5 and 10 min during carnitine or placebo infusion, at 5 min after the infusion, at the end of CPB, and at the end of the operation, i.e., approximately 1 h after weaning from CPB. Free carnitine (FC) and total carnitine (TC) plasma levels were determined as described by Rössle et al. (15).

Statistical Analysis

Data presented are mean ± SD. For statistical comparison within the groups, a multivariate analysis of variances with repeated measurement design was performed. For statistical comparison among groups 1, 2, and 3, χ^2 and nonparametric tests were performed. A P value <0.05 was accepted as statistically significant.

Results

Demographic and Surgical Data

Relevant data are summarized in Table 1. There were no significant differences among groups in age, sex, body surface area, number of associated diseases, previous cardiovascular medication, number of grafts per patient, and duration of aortic cross-clamping (i.e., ischemia time).

Table 1. Patient Characteristics

	Group 1 (placebo)	Group 2 (3 g carnitine)	Group 3 (6 g carnitine)
Number of patients	20	20	20
Sex (male/female)	19/1	17/3	19/1
Age (yr)	60 ± 9	62 ± 7	62 ± 8
Body surface area (m^2)	1.87 ± 0.12	1.86 ± 0.15	1.84 ± 0.15
Number of grafts (median [range])	3 (2–5)	3.5 (3–5)	3 (1–6)
Aortic cross-clamp time (min)	36 ± 14	27 ± 8	27 ± 11
Temperatue during anesthesia (°C)	27.8 ± 0.4	27.5 ± 0.5	27.7 ± 0.4

Data are expressed as mean ± SD.

Biochemical Data

Biochemical data are listed in Table 2. In all three groups mean myocardial tissue contents of ATP were somewhat lower in the postischemic biopsy specimens than in preischemic specimens, but this difference was not significant. Myocardial CrP content remained stable in all three groups. There were no significant differences among groups in ATP content or CrP content.

Nucleotide, nucleoside, and purine base contents and distribution were not significantly different in pre- and postischemic samples or among groups ($P > 0.05$).

Plasma concentrations of FC and TC before, during, and after infusion of carnitine or placebo are summarized in Table 3 and Figure 1. During infusion of carnitine, peak plasma levels of FC and TC were related to the dose of carnitine infused. During CPB, relatively steady-state levels of plasma concentrations of FC and TC were present (Figure 1) and persisted for about an hour after weaning from CPB.

Hemodynamic Findings

Hemodynamic effects of intravenous administration of carnitine before cardiopulmonary bypass. The infusion of 3 or 6 g carnitine induced no significant changes in any of the hemodynamic parameters measured. These data 5 min after the infusion (Table 4) are considered "control" values before the start of CPB.

Effects of carnitine on hemodynamic function during weaning from cardiopulmonary bypass. The first 15 min after cessation of CPB are considered as the "weaning

Table 2. Myocardial Levels of Markers of Tissue Ischemia

	ATP	CrP	ADP	AMP	ADE	INO	HX	X
Group 1								
Before	18.5 ± 7.0	21.7 ± 0.9	3.3 ± 0.9	0.8 ± 0.7	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.1
After	17.2 ± 5.1	21.1 ± 8.0	3.5 ± 1.2	0.8 ± 0.3	0.1 ± 0.1	0.1 ± 0.2	0.0 ± 0.1	0.0 ± 0.0
Group 2								
Before	19.3 ± 6.8	22.3 ± 10.6	3.8 ± 2.0	0.9 ± 1.0	0.0 ± 0.0	0.1 ± 0.3	0.9 ± 4.0	0.0 ± 0.1
After	17.6 ± 5.7	22.0 ± 8.5	3.5 ± 1.6	0.8 ± 0.7	0.1 ± 0.2	0.4 ± 1.2	0.7 ± 2.9	0.1 ± 0.2
Group 3								
Before	18.9 ± 5.5	21.4 ± 8.2	3.2 ± 1.1	0.6 ± 0.3	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.3	0.0 ± 0.0
After	17.5 ± 5.0	23.4 ± 7.7	3.4 ± 1.2	0.7 ± 0.5	0.1 ± 0.1	0.1 ± 0.3	0.1 ± 0.1	0.0 ± 0.1

Data are given in μmol/g dry wt, mean ± SD.

ATP, adenosine triphosphate; CrP, creatine phosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ADE, adenosine; INO, inosine; HX, hypoxanthine; X, xanthine; before, biopsy taken immediately after the onset of cardiopulmonary bypass but before the first ischemic interval; after, biopsy taken after the last ischemic interval followed by reperfusion and rewarming but before weaning from cardiopulmonary bypass.

Table 3. Plasma Concentrations of Free and Total Carnitine Before, During, and After 10 Min of Intravenous Carnitine Infusion (3 or 6 g total dose)

	Placebo	Carnitine (3 g)	Carnitine (6 g)
Plasma free carnitine			
Before infusion	38 ± 3	36 ± 7	43 ± 8
5-min infusion	36 ± 8	175 ± 258	2571 ± 900
10-min infusion	35 ± 8	2213 ± 377	4207 ± 802
5-min after infusion	36 ± 9	1506 ± 263	2741 ± 223
End of cardiopulmonary bypass	28 ± 8	434 ± 103	940 ± 254
End of operation	30 ± 6	323 ± 111	765 ± 231
Plasma total carnitine			
Before infusion	46 ± 13	47 ± 12	50 ± 7
5-min infusion	45 ± 11	1784 ± 263	3075 ± 968
10-min infusion	45 ± 10	2212 ± 376	4327 ± 885
15-min infusion	46 ± 11	1574 ± 269	2790 ± 240
End of cardiopulmonary bypass	43 ± 12	458 ± 100	964 ± 257
End of operation	40 ± 10	340 ± 102	780 ± 237

Data are given in μmol/L, mean ± SD.

Infusion was performed before the start of cardiopulmonary bypass.

phase." Measurements of hemodynamic function 1, 5, 10, and 15 min after cessation of CPB are summarized in Table 4. Mean aortic pressure, heart rate, cardiac index, pulmonary wedge pressure, and LV dP/dt_{max} values were not statistically significantly different among groups during the weaning phase. During the first minute of weaning, left ventricular cardiac work index was significantly higher in group 2, i.e., the 3-g carnitine group, than in the other two groups ($P < 0.05$). In group 2 one of 20 patients needed dopamine (>4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and four received a bolus of 0.5 g calcium intravenously. In the placebo group two of 20 patients received dopamine and five received 0.5 g calcium intravenously. In group 3, i.e., the 6-g carnitine group, three of 20 patients received dopamine and seven received 0.5 g calcium intravenously. The need for positive inotropic support did not differ significantly between groups (χ^2).

Effects of carnitine on hemodynamic function 1–24 h after cardiopulmonary bypass. The hemodynamic variables measured at 1, 6, 12, 18, and 24 h after cessation of CPB are summarized in Table 5 and Figure 2. None of the variables differed significantly among groups. The need for either positive inotropic agents or vasodilators was also not significantly different between groups (χ^2), although there was a tendency to have an increased need for support in group 3, i.e., the 6-g carnitine group.

Discussion

This study was designed to investigate possible beneficial effects of carnitine supplementation on postoperative cardiac function and metabolism in patients undergoing coronary artery bypass grafting. The theoretical background behind the concept that carnitine is able to improve clinical outcome after such an operation is well established. Every cardiac operation is associated with some degree of myocardial ischemia, and one of the important metabolic alterations during such an ischemic event is accumulation of acyl CoA in the myocardium (6). Accumulation of acyl CoA is linked to impaired adenine translocase activity in the ischemic heart (4,5), which inhibits the formation of ATP because it reduces the rate of inward transport of extramitochondrial adenosine diphosphate. It is known that carnitine reverses acyl CoA inhibition of mitochondrial adenine nucleotide translocase (12), and increased myocardial tissue levels of ATP can be found in the ischemic heart tissue of carnitine-supplemented dogs (8).

In our study we could not detect such an "ATP

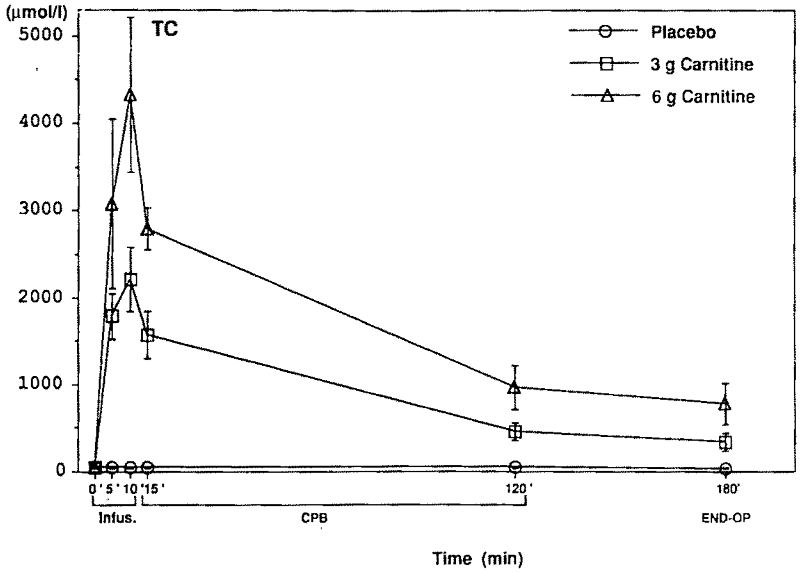

Figure 1. Plasma levels of total carnitine before, after 5 and 10 min of carnitine infusion, 5 min after infusion, at the end of CPB, and at the end of the operation. Values are mean ± SD. Time 0 h represents the preoperative control value; time 2 h represents 15 min after weaning from CPB.

Table 4. Recovery of Hemodynamic Function During Weaning From Cardiopulmonary Bypass in the Three Groups of Patients After Coronary Bypass Grafting

Parameter	Control	1 min	5 min	10 min	15 min
MAP (mm Hg)					
Group 1	80 ± 9	54 ± 10	61 ± 12	64 ± 8	65 ± 13
Group 2	76 ± 8	59 ± 12	59 ± 8	67 ± 10	67 ± 9
Group 3	78 ± 10	53 ± 12	59 ± 7	63 ± 8	64 ± 8
HR (beats/min)					
Group 1	67 ± 13	85 ± 16	86 ± 15	86 ± 15	83 ± 15
Group 2	71 ± 12	84 ± 12	82 ± 17	87 ± 17	87 ± 14
Group 3	67 ± 12	83 ± 10	85 ± 7	87 ± 9	86 ± 10
CI ($L \cdot min^{-1} \cdot m^{-2}$)					
Group 1	2.7 ± 1.1	2.7 ± 0.7	3.3 ± 0.6	3.3 ± 0.8	3.3 ± 0.9
Group 2	2.6 ± 0.5	3.1 ± 1.0	3.4 ± 0.6	3.4 ± 0.9	3.5 ± 0.7
Group 3	2.7 ± 0.6	2.8 ± 0.7	3.1 ± 0.9	3.4 ± 1.0	3.2 ± 0.7
PCWP (mm Hg)					
Group 1	7 ± 2	10 ± 3	9 ± 2	10 ± 3	10 ± 3
Group 2	7 ± 2	10 ± 2	10 ± 2	9 ± 2	10 ± 2
Group 3	7 ± 2	11 ± 2	11 ± 2	11 ± 3	11 ± 3
LV dP/dt_{max} (mm Hg/s)					
Group 1	909 ± 267	643 ± 194	758 ± 242	828 ± 304	865 ± 275
Group 2	957 ± 300	708 ± 239	768 ± 306	926 ± 229	883 ± 265
Group 3	925 ± 168	655 ± 232	791 ± 286	838 ± 335	826 ± 375
RVSWI ($g \cdot m \cdot m^{-2}$)					
Group 1	0.47 ± 0.19	0.54 ± 0.16	0.70 ± 0.16	0.73 ± 0.23	0.72 ± 0.22
Group 2	0.48 ± 0.14	0.65 ± 0.21	0.75 ± 0.13	0.67 ± 0.22	0.71 ± 0.22
Group 3	0.47 ± 0.10	0.52 ± 0.15	0.69 ± 0.18	0.71 ± 0.21	0.70 ± 0.18
LVSWI ($g \cdot m \cdot m^{-2}$)					
Group 1	2.84 ± 1.06	1.93 ± 0.56	2.72 ± 0.67	2.85 ± 0.74	2.93 ± 0.90
Group 2	2.68 ± 0.68	2.59 ± 1.15[a]	2.76 ± 0.71	3.04 ± 0.92	3.11 ± 0.76
Group 3	2.86 ± 0.72	2.08 ± 0.71	2.53 ± 0.96	2.91 ± 1.02	2.81 ± 0.70
SVR ($dyne \cdot s \cdot cm^{-5}$)					
Group 1	1374 ± 508	812 ± 247	738 ± 224	818 ± 218	816 ± 284
Group 2	1231 ± 233	756 ± 292	652 ± 199	822 ± 267	790 ± 217
Group 3	1248 ± 298	737 ± 217	775 ± 182	786 ± 264	811 ± 228

Data are given as mean ± SD.

MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; PCWP; pulmonary capillary wedge pressure; LV dP/dt_{max}, first derivative of the left ventricular pressure; RVSWI, right ventricular stroke work index; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance.

Group 1, placebo; group 2, pretreatment with 3 g carnitine; and group 3, pretreatment with 6 g carnitine.

[a] $P < 0.05$ compared with group 1 values.

Table 5. Hemodynamic Function 1–24 h After Cardiopulmonary Bypass

Parameter	Control	1 h	6 h	12 h	18 h	24 h
MAP (mm Hg)						
Group 1	80 ± 9	79 ± 14	80 ± 15	73 ± 10	75 ± 10	81 ± 11
Group 2	76 ± 8	75 ± 11	78 ± 12	73 ± 7	78 ± 10	83 ± 12
Group 3	78 ± 10	81 ± 15	79 ± 11	74 ± 16	78 ± 10	81 ± 15
HR (beats/min)						
Group 1	67 ± 13	84 ± 15	92 ± 11	85 ± 14	86 ± 15	85 ± 11
Group 2	71 ± 12	90 ± 11	94 ± 12	85 ± 17	84 ± 15	84 ± 13
Group 3	67 ± 12	90 ± 11	88 ± 11	84 ± 12	84 ± 12	81 ± 15
CI ($L \cdot min^{-1} \cdot m^{-2}$)						
Group 1	2.7 ± 1.1	3.2 ± 0.7	3.1 ± 0.7	3.0 ± 0.5	3.2 ± 0.7	3.2 ± 0.6
Group 2	2.6 ± 0.5	3.1 ± 0.6	3.2 ± 0.5	3.2 ± 0.7	3.2 ± 0.5	3.1 ± 0.6
Group 3	2.7 ± 0.6	3.0 ± 0.6	3.5 ± 0.5	3.1 ± 0.6	3.2 ± 0.5	3.2 ± 0.6
PCWP (mm Hg)						
Group 1	7 ± 2	9 ± 3	10 ± 3	9 ± 4	10 ± 4	10 ± 3
Group 2	7 ± 2	9 ± 2	9 ± 3	10 ± 3	9 ± 2	9 ± 3
Group 3	7 ± 2	8 ± 4	8 ± 3	10 ± 3	9 ± 4	10 ± 3
RVSWI ($g \cdot m \cdot m^{-2}$)						
Group 1	0.47 ± 0.19	0.71 ± 0.18	0.80 ± 0.22	0.72 ± 0.17	0.72 ± 0.28	0.77 ± 0.24
Group 2	0.48 ± 0.14	0.66 ± 0.21	0.79 ± 0.28	0.73 ± 0.22	0.76 ± 0.21	0.79 ± 0.26
Group 3	0.47 ± 0.10	0.67 ± 0.21	0.83 ± 0.24	0.81 ± 0.25	0.79 ± 0.25	0.84 ± 0.29
LVSWI ($g \cdot m \cdot m^{-2}$)						
Group 1	2.84 ± 1.06	3.48 ± 0.95	3.49 ± 1.00	2.94 ± 0.61	3.30 ± 1.00	3.53 ± 0.88
Group 2	2.68 ± 0.68	23.13 ± 0.67	3.42 ± 0.82	3.14 ± 1.00	3.38 ± 0.66	3.60 ± 1.24
Group 3	2.86 ± 0.72	3.29 ± 0.67	3.71 ± 0.80	3.08 ± 0.94	3.46 ± 0.81	3.60 ± 1.16
SVR ($dyne \cdot s \cdot cm^{-5}$)						
Group 1	1374 ± 508	998 ± 258	1026 ± 275	949 ± 207	954 ± 214	1027 ± 253
Group 2	1231 ± 233	992 ± 297	958 ± 197	907 ± 204	973 ± 207	1070 ± 273
Group 3	1248 ± 298	1130 ± 371	924 ± 208	931 ± 260	946 ± 162	981 ± 209

Data are given as mean ± SD.
Abbreviations as in Table 4.

sparing" effect of carnitine supplementation. Indeed, we analyzed myocardial biopsy specimens for their high-energy phosphate content and did not find better preservation of ATP in the carnitine-supplemented groups. However, the absence of changes in total tissue stores of ATP and CrP neither proves nor disproves the "improvement in adenine nucleotide translocase" of carnitine. This would require a detailed knowledge of intracellular distribution of products of, and the exact location of pools of, critical adenosine intermediates. Such methods of measurement are currently unavailable for intact tissue (9).

Nevertheless, when a beneficial effect of carnitine supplementation on myocardial ATP and CrP contents is not detectable, a clinically significant improvement of postischemic cardiac function might still occur. In the present study, however, we were not able to detect any significant effect of carnitine pretreatment on the recovery of cardiac function after coronary artery bypass surgery. This is in contrast to the conclusion of another study in patients undergoing aortocoronary bypass grafting who received oral carnitine supplementation before surgery (16). In that study, a significantly reduced postoperative need for positive inotropic support was found in carnitine-treated patients. However, it cannot be concluded from that study that the improvement of postoperative cardiac function was related to improvement of mitochondrial energy production: myocardial tissue contents of ATP were higher in the carnitine-supplemented group than in the placebo group, but postischemic ATP levels were not determined. In an experimental study using ischemic swine hearts it was also shown that carnitine is capable of preserving mechanical function (9), presumably by modifying the toxic effects of accumulated free fatty acid intermediates. However, a mode of action of carnitine not involving a primary metabolic effect remains possible because carnitine is an inotropic agent and can increase coronary blood flow (17).

An essential question is whether the doses of carnitine selected in the present study are adequate, when injected intravenously, to produce biochemically or pharmacologically effective concentrations in the myocardium. Although we did not measure myocardial tissue concentrations of carnitine in our patients, we know from previous reports (18) that the net uptake of infused carnitine by muscle tissue is

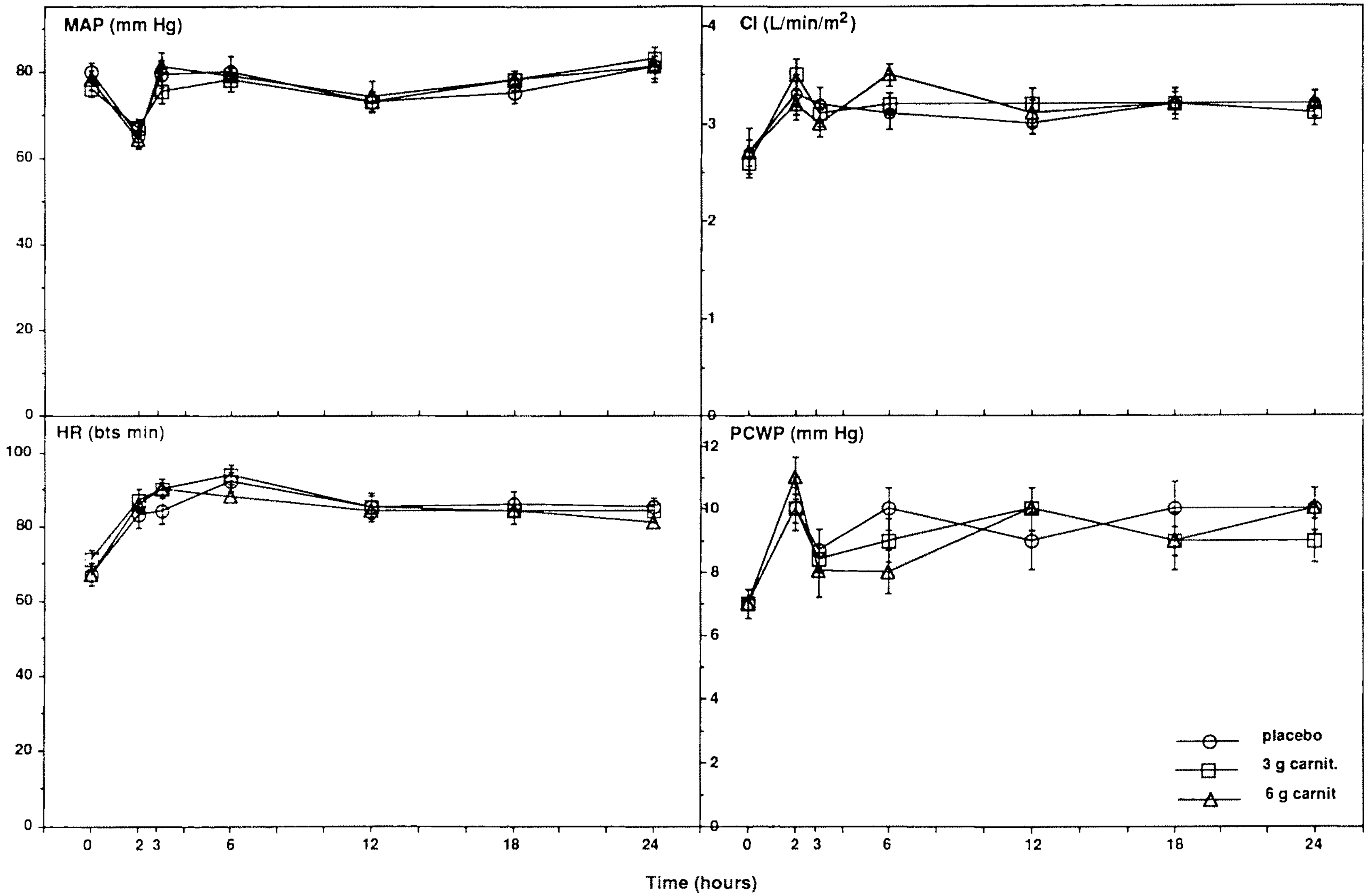

Figure 2. Effects of IV carnitine on hemodynamic measurements after aortocoronary bypass surgery. *Upper panel left:* mean aortic pressure (MAP); *upper panel right:* cardiac index (CI); *lower panel left:* heart rate (HR); *lower panel right:* pulmonary capillary wedge pressure (PCWP). Values are mean ± SD. Time 0 h represents the preoperative control value; time 2 h represents 15 min after weaning from CPB.

very low: a daily infusion of 0.75 g total dose (74 μmol·kg^{-1}·day^{-1}) resulted in a doubling of the plasma concentrations of free and total carnitine, and the acylcarnitine/free carnitine ratio dropped to about 50% of its initial value. The authors calculated that the total muscle tissue carnitine concentration increased only approximately 0.1 μmol/g wet wt. Muscle tissue carnitine concentrations were 25.2 and 28.9 μmol/g for FC and TC, respectively. In another study (19), the effects of a 4-h infusion of 1.2 g (total dose) carnitine were assessed; plasma levels of FC and TC after the infusion were found to be 4.5 and 4.2 times higher, respectively, than preinfusion values. In our present study, we used total doses of 3 and 6 g carnitine, infused during a 10-min period before starting CPB. In the group supplemented with 3 g carnitine, plasma levels of FC and TC increased to 41 and 33 times control values, respectively, at 5 min after infusion. In the group supplemented by 6 g carnitine these values increased to 63 and 55 times control values for FC and TC, respectively. Because the injected carnitine was diluted by the volume of the cardiopulmonary perfusion equipment at initiation of CPB, we determined plasma levels again at the end of CPB, approximately 130 min after the start of the infusion. At this time, plasma levels were still 12 and 10 times higher than control values for FC and TC, respectively, in the 3-g carnitine-supplemented group, and 22 and 20 times higher than control values for FC and TC, respectively, in the 6-g carnitine-supplemented group. Therefore, it can be expected that muscle tissue levels of carnitine also increased considerably in our patients. On the other hand, plasma and urinary carnitine levels are not reliable indicators of the capacity for intramitochondrial fat oxidation (20). Indeed, recent studies have shown that, in contrast to the expected carnitine-mediated promotion of lipid utilization, acute infusion of carnitine resulted in a reduction of fat oxidation. Such an impairment of fat oxidation by excess amounts of carnitine has been recently demonstrated in rats (21). It has been suggested that high levels of carnitine may increase the formation of intramitochondrial fatty acid-carnitine conjugates and their transport out of the matrix space, which means withdrawal of activated substrates for β-oxidation. It has been demonstrated in postoperative patients that this reduced rate of fat oxidation during infusion of carnitine is accompanied by an increased rate of protein oxidation (19,20), and for this reason it has been recommended that smaller amounts of carnitine be used in order to optimize fat utilization.

In a recent paper, a dose-dependent detrimental effect of carnitine upon the ischemic rat myocardium was demonstrated when carnitine was added to a cardioplegic solution (22). In our study in humans, however, no detrimental effect of carnitine pretreatment on postischemic recovery of function was seen, even with the high dose of carnitine used. Furthermore, the infusion of carnitine at both dose levels before ischemia had no effect on hemodynamic or cardiac function. This was also found in another study (12).

The overall conclusion of this double-blind, placebo-controlled study is that a beneficial effect of IV supplementation of carnitine on recovery of cardiac function and postischemic myocardial tissue contents of high energy phosphates is not apparent.

We would like to thank P. Fürst, MD, PhD, from the Institut für biologische Chemie und Ernährungs-Wissenschaft, Universität Hohenheim, Stuttgart, Germany, for the assessment of plasma free and total carnitine.

References

1. Fritz IB. Carnitine and its role in fatty acid metabolism. Adv Lipid Res 1963;1:285–334.
2. Bressler R. Physiological-chemical aspects of fatty acid oxidation. In: Wakil SJ, ed. Lipid metabolism. New York: Academic Press, 1970:49–77.
3. Neely JR, Rovetto MJ, Whitmer JT. Rate-limiting steps of carbohydrate and fatty acid metabolism in ischemic hearts. Acta Med Scand 1976;587(Suppl):9–12.
4. Shug AL, Shrago E, Bittar N, Folts JD, Koke JR. Acyl-CoA inhibition of adenine nucleotide translocation in ischemic myocardium. Am J Physiol 1975;228:689–92.
5. Shrago E, Shug AL, Sul H, Bittar N, Folts JD. Control of energy production in myocardial ischemia. Circ Res 1976;38(Suppl 1):75–82.
6. Opie LH. Role of carnitine in fatty acid metabolism of normal and ischemic myocardium. Am Heart J 1979;97:375–88.
7. Shug AL, Koke JR, Folts JF, Bittar N. Role of adenine nucleotide translocase in metabolic change caused by ischemia. In: Roy PE, Rona G, eds. The metabolism of contraction. Baltimore, Md.: University Park Press, 1975:365–78.
8. Folts JF, Shug AL, Koke JR, Bittar N. Protection of the ischemic dog myocardium with carnitine. Am J Cardiol 1979;41:1209–14.
9. Liedke AJ, Nellis SH. Effects of carnitine in ischemic and fatty acid supplemented swine hearts. J Clin Invest 1979;64:440–7.
10. Suzuki X, Kamikawa T, Yamazaki N. Effects of L-carnitine on ventricular arrhythmias in dogs with acute myocardial ischemia and supplement of excess of free fatty acids. J Circ J 1981;45:552–9.
11. Di Palma JR, Ritchie DM, McMichael FR. Cardiovascular and arrhythmic effects of carnitine. Arch Int Pharmacodyn 1975; 217:246–50.
12. Thomsen JH, Shug AL, Yap VU, Patel AK, Karras TJ, De Felice SL. Improved pacing tolerance of the ischemic human myocardium after administration of carnitine. Am J Cardiol 1979; 43:300–6.
13. Flameng W, Daenen W, Borgers M. Cardioprotective effect of Lidoflazine during one hour normothermic global ischemia. Circulation 1981;64:796–807.

14. Wijnants J, Van Belle H. Single-run high performance liquid chromatography of nucleotides, nucleosides, and major purine bases and its application to different tissue extracts. Anal Biochem 1985;144:258–66.

15. Rössle C, Kohse KP, Franz HE, Fürst P. An improved method for the determination of free and esterified carnitine. Clin Chim Acta 1985;149:263–8.

16. Böhler H, Noppeney T, Akcetine Z, Rein J, von der Emde J. The effect of preoperative L-carnitine supplementation on myocardial metabolism during aortocoronary bypass grafting. Z Kardiol 1987;76(Suppl):14–8.

17. Brooks H, Goldberg L, Holland R, Klein M, Sanzani W, De Felice SL. Carnitine induced effects on cardiac and peripheral hemodynamics. J Clin Pharmacol 1977;17:561–8.

18. Pichard C, Roulet M, Rössle C, et al. Effects of L-carnitine supplemented total parenteral nutrition on lipid and energy metabolism in postoperative stress. JPEN 1988;12:555–62.

19. Pichard C, Roulet M, Schutz Y, et al. Clinical relevance of L-carnitine-supplemented total parenteral nutrition in postoperative trauma. Metabolic effects of continuous or acute carnitine administration with special reference to fat oxidation and nitrogen utilization. Am J Clin Nutr 1989;49:283–9.

20. Roulet M, Pichard C, Rössle C, et al. Adverse effects of high dose carnitine supplementation of total parenteral nutrition on protein and fat oxidation in the critically ill. Clin Nutr 1989;8:83–7.

21. Böhler H, Akcetin Z. Ketogenic effects of low and high levels of carnitine during parenteral nutrition in the rat. Am J Clin Nutr 1987;46:47–51.

22. Hearse DJ, Shattock MJ, Manning AS, Braimbridge MW. Protection of the myocardium during ischemic arrest: possible toxicity of carnitine in cardioplegic solutions. J Thorac Cardiovasc Surg 1988;28:253–8.

A Rabbit Model for Evaluation of Spinal Anesthesia: Chronic Cannulation of the Subarachnoid Space

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LANGERMAN L, CHAIMSKY G, GOLOMB E, TVERSKOY M, KOOK AI, BENITA S. A rabbit model for evaluation of spinal anesthesia: chronic cannulation of the subarachnoid space. Anesth Analg 1990;71:529–35.

A rabbit model for evaluation of spinal anesthesia is presented. Chronic cannulation of the subarachnoid space was performed in 44 rabbits using the translumbar approach. An autopsy was performed 24 h after the operation on four of the animals. Intrathecal injections of methylene blue did not reveal any leakage from the spinal space. X-ray examination performed on the second and 30th days after the implantation indicated free spread of the injected solution in the subarachnoid space without any obstruction. Repeated injections of four identical doses of bupivacaine at 3-day intervals showed reproducible pharmacologic effects. Administration of different doses of the anesthetic produced a clear dose-response relationship. The relative activity of the anesthetic agents was found to be identical to that previously obtained in humans. No significant complications after the implantation have been recorded. We suggest the current model as an additional appropriate tool for the investigation of spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES, SPINAL, experimental model.

The wide use of spinal anesthesia and analgesia has led to the development of animal models to evaluate the physiologic and pharmacologic effects induced by the subarachnoid administration of local anesthetics and opioids (1–6).

Discrepancies among data obtained from different species (7,8) require caution in their extrapolation to humans. Continuous monitoring of respiratory and hemodynamic parameters, as well as prolonged pharmacokinetic studies during spinal anesthesia in small animals such as rats (1,4), is limited by technical difficulties. The use of larger animals, i.e., dogs (2), sheep (6), or monkeys (3), is restricted by financial considerations. The aim of this study was to develop an inexpensive model appropriate for evaluation of the effects of spinal anesthesia. The relative ease of monitoring hemodynamic and respiratory parameters in the rabbit (9), as well as the availability of blood (9) and cerebrospinal fluid (CSF) (5) samples for pharmacologic analysis, led us to choose this species for our model.

Methods and Materials

Experiments reported here were performed in accordance with the laws and guidelines established by the local Committee of Laboratory Animal Care.

Animals

Adult male rabbits of a mixed strain, weighing 2.5–3.0 kg, were used in this study. Animals were housed individually in standard cages, had free access to food and tap water, and were kept on a 12-h light-dark cycle.

Catheter Preparation

Polyvinyl catheters 300 mm long with an outer diameter of 0.61 mm and an inner diameter of 0.28 mm (Dural Plastics & Engineering PTY, Ltd.) were used for the procedure. A ring from the tip of a Luer-type

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Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from the Department of Pharmacy, School of Pharmacy, the Hebrew University, Jerusalem, Israel; the Department of Anesthesiology, Rebecca Sieff Government Hospital, Safed, Israel; and the Department of Orthopedics, Hadassah University Hospital, Jerusalem, Israel. Accepted for publication July 11, 1990.

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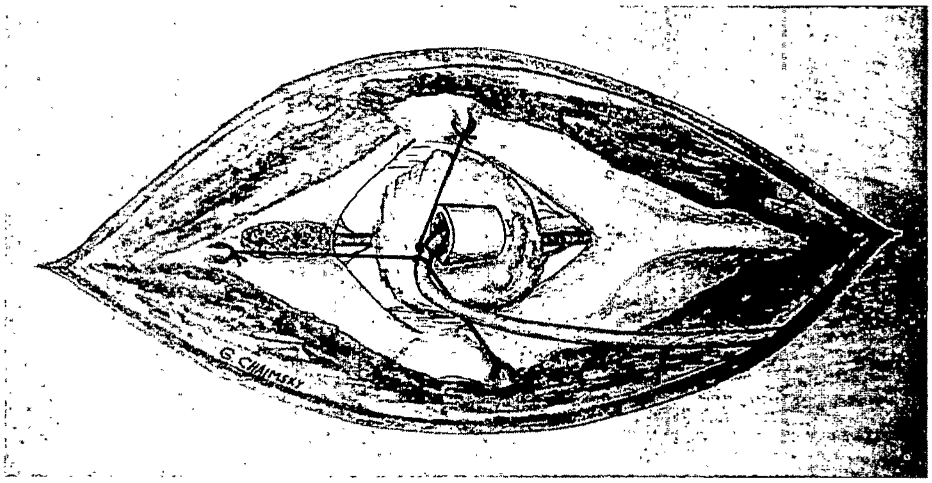

Figure 1. Schematic illustration of the fixation of the catheter in the subarachnoid space. The tip of the catheter is placed in the cephalad direction. A fixation device, a plastic ring, is bound to the periosteum of the lamina by three nylon 5/0 sutures.

plastic syringe, cut 3 mm from the end, was used as a device for fixation. The distal end of the catheter was passed through the cut piece of a plastic ring and sealed inside with epoxy glue 20 mm from the tip. A nylon monofilament suture (Ethycon 5/0) 10 cm long was tied around the catheter 30 mm from the proximal end and fixed with epoxy glue. The dead space of the catheters, evaluated by filling them with normal saline, ranged between 13 and 15 μL, and never exceeded 18 μL. Before implantation, the catheters were disinfected in 70% alcohol (including inside filling) and then flushed with normal saline. The proximal tip of the catheter was closed with a stainless steel plug.

Preoperative Procedures

Animals were premedicated with 50 mg/kg ketamine subcutaneously and placed in a restraining hammock on the operating table in the prone position. The table was placed in the head-up position to promote lumbar CSF accumulation. The surgical fields in the dorsal cervical and lumbar areas were shaved and cleaned with 0.5% chlorhexidine in 70% alcohol solution.

Three milliliters of 0.5% bupivacaine containing adrenaline (1:200,000) were injected subcutaneously over the line between the sixth lumbar and first sacral spinous processes, and 1.0 mL was injected over the base of the seventh lumbar process.

The marginal ear vein was cannulated, and ketamine was continuously infused intravenously at a rate of 1–1.5 $\mathrm{mg \cdot kg^{-1} \cdot min^{-1}}$, using a pump.

Surgery

Surgical procedures were performed under aseptic conditions. The skin and subcutaneous fascia were opened by a straight midline incision, between the sixth lumbar and first sacral spinous processes. Muscles from both sides of the seventh lumbar spinous process were separated by blunt dissection. The process, ligamentum flavum, and epidural fat were sequentially removed, and the underlying transparent dura with the spinal cord was exposed. A piece of the subcutaneous fascia was separated and the distal tip of the catheter was passed through this piece up to the plastic ring fixed previously. Using an operating microscope, fine forceps, and a 25-gauge needle, a small slit was made in the dura and arachnoid membranes until leakage of CSF was detected. The distal end of the catheter was inserted subarachnoidally in a caudad direction. The catheter was fixed above the plastic probe to the periosteum of the posterior lamina (Figure 1). The external part of the catheter was stretched through a subcutaneous tunnel along the back and exteriorized via an incision on the neck. A suture previously glued 30 mm from the tip of the catheter was tied to a buttonlike polyethylene disk and then fixed to the internal surface of the skin with an additional suture (Figure 2). The tip of the catheter was extracted via an additional hole near the disk, and the incision was closed with Dexon 4/0 sutures.

Experimental Design

Twenty-four hours after the operation the animals were examined. Because none of the rabbits operated on showed signs of discomfort or neurologic deficits,

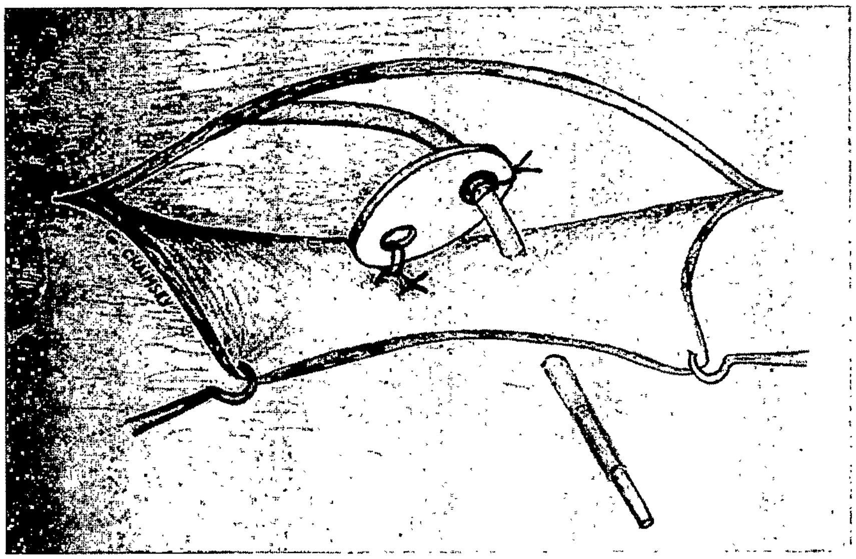

Figure 2. Schematic illustration of the external part of the catheter fixed in the subcutaneous area of the dorsal neck surface. The proximal part of the catheter is bound to a plastic disk, which is affixed by suture to the subcutaneous fascia.

all were used in the study. Forty-four animals were randomly divided into eight groups. Randomization of the allocation of animals to experimental groups was performed by the use of a random number table. Four animals were used for examination of the leakage from the site of the catheter implantation 24 h after the operation (group 1). Four animals were used for examination of the spread of a contrast liquid in the subarachnoid space on the second and 30th days after the operation (group 2). Six animals were used for evaluation of the variability in the pharmacologic effect produced by repeated spinal injections of equal doses of an anesthetic (group 3). Six animals were selected for assessment of the dose-response relationship to three different doses of anesthetic (group 4). Four groups of six animals each served for a comparative evaluation of the relative anesthetic activity of amethocaine, bupivacaine, lidocaine, and procaine (groups 5–8, respectively).

All the injections were followed by irrigation of the catheter with 50 μL of distilled water to avoid catheter obstruction. In all the animals used for prolonged studies the catheters were flushed every 72 h.

Revision of the Implantation Site for the Existence of Leakage

Twenty-four hours after the operation, methylene blue (100 μL/kg) was injected through the catheter in four rabbits. The animals were killed by overdose of thiopental. The operation wound was reopened, and the area of the implantation was exposed. After removal of the catheter, the area around the site of implantation was carefully examined.

Myelography

X-ray examinations after the intrathecal administration of metrizamide (100 μL/kg) were performed in four rabbits, 24 h and 30 days after the operation, to assess the spread of the contrast liquid in the spinal space.

Evaluation of the Pharmacologic Effect

Because it was not possible to evaluate sensory blockade accurately in the current model, the pharmacologic action of anesthetics was assessed by estimation of the motor block duration produced by the injected agent. Motor ability was evaluated by observation of the disturbances in walking, using criteria similar to those suggested by Feldman and Covino in dogs (2). In order to quantify the anesthetic action, the motor blockade was graded using a modification of the scale proposed by Bromage (10). The degree of motor blockade was evaluated at 5-min intervals. Free movements of the animal using hind limbs without limitation or loss of balance was designated as 0, limited or asymmetrical movements of the hind limbs in order to support the body and walk as I, inability to support the back of the body on hind limbs with detectable ability to move the limbs and respond to pain stimulus as II, and total paralysis of the hind limbs as III.

Evaluation of Variability of the Pharmacologic Action in Response to Repeated Injections of Bupivacaine

Four repeated intrathecal injections of 0.5% bupivacaine in the dose of 250 μg/kg were administered in six rabbits at 3-day intervals. The time interval between the end of each injection and full recovery of the motor activity was defined as the duration of the blockade.

Dose-Response Relationship

Three consecutive increasing doses of bupivacaine (62.5, 125, and 250 mg/kg) were administered intrathecally in six rabbits at 72-h intervals. Motor block was assessed after each administration. This regime was repeated twice.

Comparative Evaluation of Four Different Local Anesthetics

One percent solutions of amethocaine, bupivacaine, lidocaine, and procaine were administered intrathecally in doses of 500 mg/kg in four groups of rabbits. The duration of the motor blockade was evaluated after each injection.

Statistical Analysis

Data are presented as mean ± SEM. Comparisons between effects produced by injections of local anesthetic were performed using analysis of variance, followed by *t*-tests between pairs of groups.

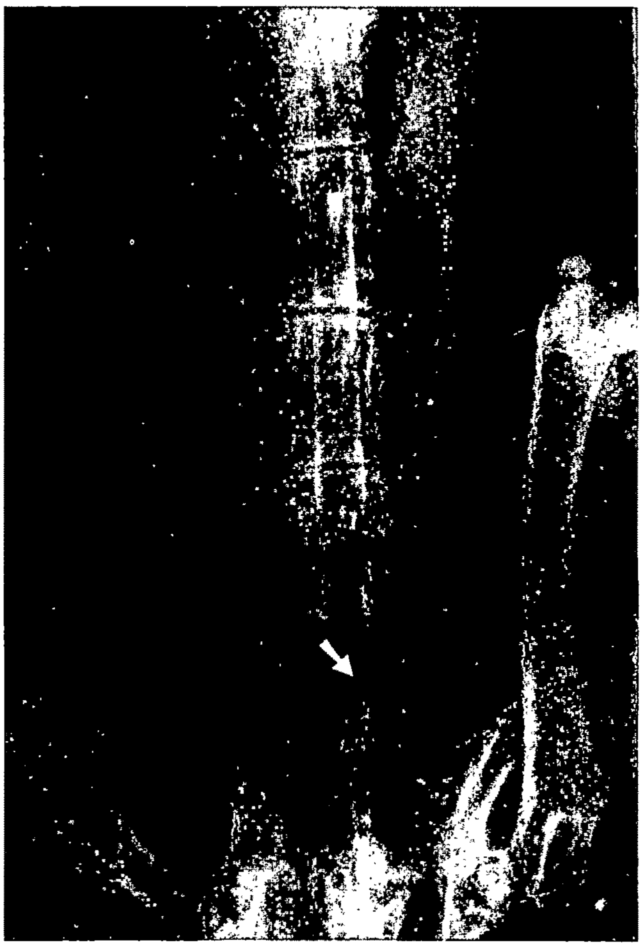

Figure 3. Photograph of a roentgenogram 5 min after spinal administration (300 μL) of the water-soluble contrast agent metrizamide 30 days after catheter implantation. *Arrow* points to the level of the tip of the catheter.

Results

Within 1 h after surgery all the animals studied were awake and moving actively using all limbs. The injection procedure was easily tolerated, and the animals did not show signs of discomfort during the period of investigation. No systemic adverse effects were recorded in any of the animals.

Observation of the site of catheter implantation 24 h after the operation revealed organized blood clots and fibrin around the piece of fascia that we placed around the catheter. Release of the sutures and removal of the catheter was accompanied by leakage of blue fluid (methylene blue dissolved in CSF) from the hole in the dura. Hence, effective hermetic closure of the implanted catheter was observed 24 h after the operation. Therefore, autopsies after the operation were not indicated.

Radiographic examinations on the second and 30th days after the operation showed free spread of the contrast liquid in both directions from the implanted catheter (Figure 3), and no leakage was observed at the site of injection in any of the animals studied.

Four repeated intrathecal administrations of bupivacaine at 3-day intervals produced equal duration of motor blockade. No statistically significant difference was found between injections. Mean periods of duration of the motor blockade produced by the first, second, third, and fourth injections are demonstrated in Figure 4.

No significant difference was found between effects produced by equal doses of the local anesthetic (group 3). Administration of increasing doses of bupivacaine in the same animals produced clear augmentation of the pharmacologic action. Statistically significant differences were found among the values yielded by the three different doses. The results are presented graphically in Figure 5.

Subarachnoid administration of a 1% solution of either amethocaine, bupivacaine, or lidocaine pro-

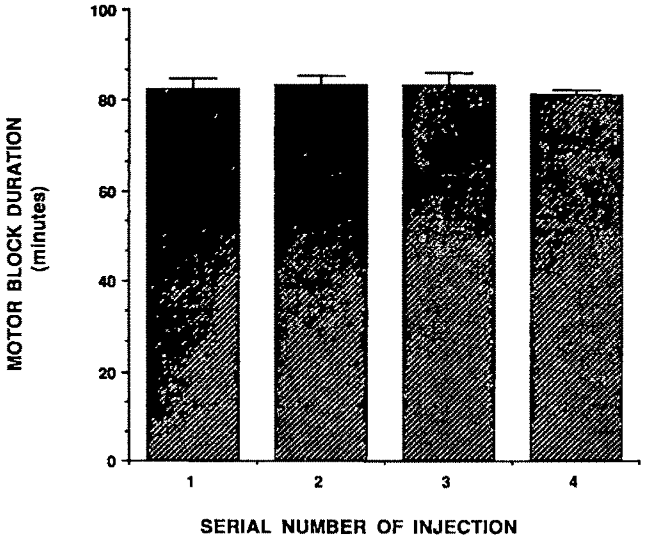

Figure 4. Duration of motor blocks produced by repeated spinal injections of bupivacaine. The serial number of the injection is presented on the horizontal axis, and the mean duration of the motor blockade is shown (in min) on the vertical axis. The error bars represent SEM, $n = 6$.

duced clear motor blockade in all the animals studied. However, a 1% solution of procaine failed to produce complete paralysis, and therefore an additional experiment using 2% solution of the drug was employed. Statistically significant differences in the pharmacologic action were observed among the anesthetic agents studied. The order of relative activity of the drugs evaluated was amethocaine > bupivacaine > lidocaine > procaine. Results dealing with the pharmacologic effect produced by the four different drugs are demonstrated graphically in Figure 6.

Discussion

Different approaches have been used for chronic cannulations of the subarachnoid space in animal models. The use of direct transcutaneous cannulation is restricted to large animals. Chronic implantation of spinal catheters was described in small animals; the atlanto-occipital approach (1), as well as a translumbar route (4), was successfully used for this purpose. In rabbits the translumbar approach for cannulation of the epidural space was described by Durant and Yaksh (11). In the current study the same approach was used, but an additional procedure—removal of the ligamentum flavum and epidural fat—provided convenient conditions for visualization of the spinal cord and facilitated relatively atraumatic cannulation of the subarachnoid space.

Injections of methylene blue through the catheter, followed by autopsy of the animals and examination of the implantation site, showed absence of CSF leakage as early as 24 h after the operative procedure, providing evidence that nearly all of the injected drug was available to the target tissue. Myelography confirmed this finding and, moreover, showed free spread of the contrast solution in both directions from the implanted catheters. This finding indicates an advantage of the present model over rat models. In the rat models (1,4) subarachnoid implantation of the catheter is accompanied by obstruction of the spinal

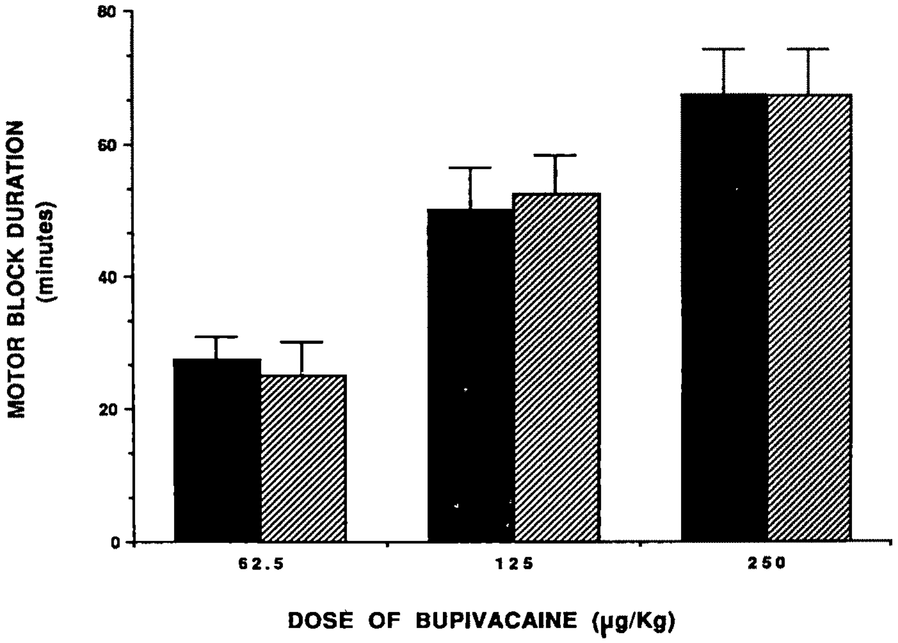

Figure 5. Duration of the motor blockade produced by bupivacaine: a dose-response relationship. Each animal ($n = 6$) received each dose twice. The dark and light bars represent the mean responses to the first and second injection of the dose, respectively. Error bars represent SEM. Statistically significant differences were found among three doses employed.

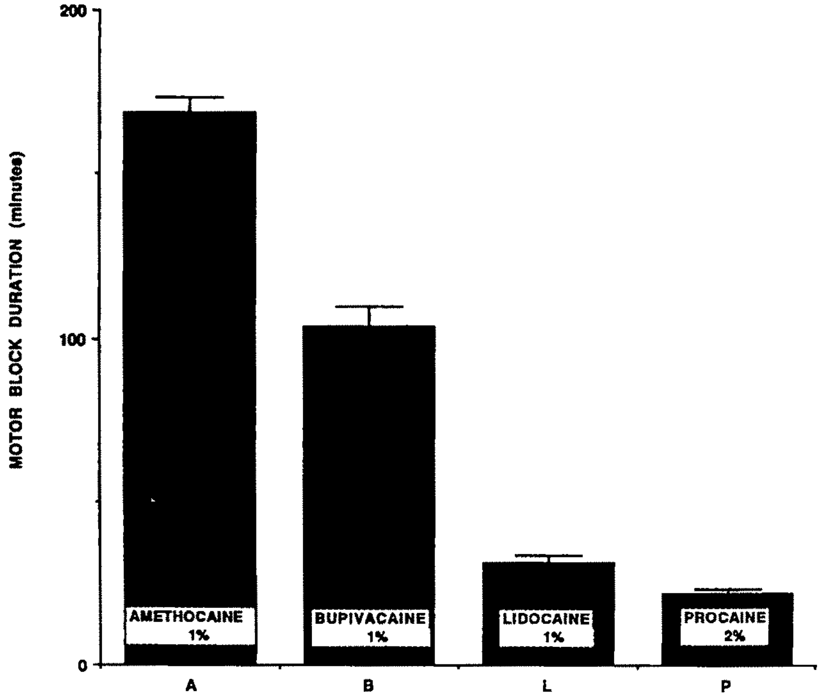

Figure 6. Duration of the motor blockades produced by four local anesthetics. Amethocaine, bupivacaine, and lidocaine were used in equal doses (1%–50 μL/kg). Because 1% solution of procaine failed to produce complete block, a 2% solution of the drug was employed. Error bars represent SEM. Statistically significant differences were found between every pair of solutions.

space and therefore the spread of injected solution has been unidirectional. It seems that the piece of fascia placed around the tip of the catheter induces adhesions and fibrin organization, which covers the slit in the dura and prevents the leakage of CSF. The absence of leakage prevents major anatomic disturbances around the site of the implantation—namely, adhesions around the spinal cord and compression of the dura—and permits free spread of CSF in both directions from the implanted catheter.

The reproducibility of the pharmacologic effect of spinal anesthesia and the precise dose-response relationship was demonstrated in groups 3 and 4, respectively. This finding enables the design of sequential experiments in which each animal serves as its own control. Hence, an accurate result may be provided by a relatively small number of animals.

Differences clearly exist between humans and rabbits in the anatomy of the subarachnoid space and methods of performing spinal anesthesia. Therefore, we decided to assess the order of relative anesthetic activity of four agents and to compare this order with results obtained in humans. The relative anesthetic activity evaluated by the duration of the motor blockade in the current model was identical to data previously reported in humans (12).

In summary, the following principal properties of the model presented are noted.

1. No leakage of the injected solutions from the spinal space was observed up to 30 days after the implantation of the catheter.
2. Free spread of the injected solution in the spinal space was observed up to 30 days after the implantation of the catheter.
3. Reproducible pharmacologic effect was produced by four repeated injections of the anesthetic at 72-h intervals.
4. A clear dose-response relationship was found after administration of different doses of a local anesthetic.
5. Comparative anesthetic activity of four local anesthetics assessed in the present model was identical to that observed in humans.

Hence, we suggest the current model as an appropriate additional tool for further investigation of spinal anesthesia.

The authors acknowledge the valuable assistance and cooperation provided by nurses Hannah Friedman of Jerusalem and Denise L. White of Columbia, South Carolina, without whose help and support this project could not have been completed as efficiently as it was.

References

1. Yaksh TL, Rudy TA. Chronic catheterization of the spinal subarachnoid space. Physiol Behav 1976;17:1031–6.
2. Feldman HS, Covino BG. A chronic model for investigation of experimental spinal anesthesia in the dog. Anesthesiology 1981;54:148–52.
3. Denson DD, Briedenbaugh PO, Phero JC, Raf PP, Turner PA,

Ohlweiler DF. Evaluation of lidocaine spinal anesthesia in the rhesus monkey. Anesth Analg 1981;60:759–69.

4. Bahar M, Rosen M, Vickers MO. Chronic cannulation of the intradural or extradural space in the rat. Br J Anaesth 1984;56: 405–10.
5. Wang BC, Hiller JM, Holland MJ, Simon EJ, Hillman DE, Turndorf H. Distribution of ^{3}H-morphine following lumbar subarachnoid administration in rabbits. Anesthesiology 1989; 70:817–24.
6. Payne R, Intrussi CE. CSF distribution of morphine, methadone and sucrose after intrathecal injection. Life Sci 1985;37: 1137–44.
7. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous local anesthetics in anesthetised ventilated dogs. Anesth Analg 1982;61:317–22.
8. Chadwick HS. Toxicity and resuscitation in lidocaine or bupivacaine-infused cats. Anesthesiology 1985;63:385–90.
9. Hovav E, Weinstock M. Temporal factors influencing the development of acute tolerance to opiates. J Pharmacol Exp Ther 1987;242:251–6.
10. Bromage AR. Epidural analgesia. Philadelphia: WB Saunders, 1978:308.
11. Durant PAC, Yaksh TL. Epidural injection of bupivacaine, morphine, fentanyl, lofentanyl and DADL in chronically implanted rats: a pharmacologic and pathologic study. Anesthesiology 1986;64:43–53.
12. Covino BG. Pharmacology of local anesthetic agents. Br J Anaesth 1986;58:701–16.

Is the Antiemetic Effect of the Emulsion Formulation of Propofol Due to the Lipid Emulsion?

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ÖSTMAN PL, FAURE E, GLOSTEN B, KEMEN M, ROBERT MK, BEDWELL S. Is the antiemetic effect of the emulsion formulation of propofol due to the lipid emulsion? Anesth Analg 1990;71:536–40.

The hypothesis that the lipid emulsion of the emulsion formulation of propofol is responsible for the low frequency of nausea, retching, and vomiting after propofol anesthesia was tested. A randomized, prospective, and comparative study was performed to evaluate the antiemetic effect of 10% lipid solution in 60 women, ASA physical status I and II, scheduled for ambulatory laparoscopic procedures. Two groups of patients were studied. Induction of anesthesia (thiopental) and maintenance of anesthesia (enflurane, nitrous oxide) were similar in both groups. At induction the study group received 10% Intralipid (3 mL/min for 20 min). The control group received 5% dextrose in lactated Ringer's solution at the same rate. Other drugs administered during or after anesthesia were similar among the groups. The groups were similar with respect to duration of anesthesia, characteristics of early and intermediate recovery, as well as pain scores in the postanesthesia care unit. There were no differences in the amount of antiemetic medications administered or postoperative nausea, retching, or vomiting when the patients were evaluated objectively by a blinded observer or subjectively by patient self-evaluation. It is concluded that 10% Intralipid, the lipid in the emulsion formulation of propofol, does not possess significant antiemetic effects.

Key Words: ANESTHETICS, INTRAVENOUS—propofol.

Postoperative nausea and vomiting are a common problem after general anesthesia. They are a major cause of prolonged recovery time and delayed discharge from the hospital in ambulatory surgical patients.

Propofol is a phenol hypnotic used for induction and maintenance of anesthesia. It is well-suited for short procedures because of rapid induction and recovery times (1). Propofol was originally formulated in Cremophor EL as a 1% or 2% solution (2). Postoperative nausea and vomiting were not specifically studied in the early literature, although O'Callaghan et al. (3) found no differences in the incidence of nausea or vomiting when propofol anesthesia was compared with alphadione anesthesia. Cremophor EL was eventually abandoned due to significant pain on injection and reports of serious anaphylactoid reactions (4).

In the early 1980s, propofol was reformulated in a lipid emulsion (Intralipid, 10% soya bean oil, 1.2% egg phosphatide, 2.25% glycerol). Several recent studies have shown a reduced propensity for postoperative nausea and vomiting in patients receiving propofol in lipid emulsion compared with other anesthetic agents (5–7).

Based on the lack of specific information about the antiemetic effect of the early Cremophor EL formulation of propofol, we hypothesized that the fat emulsion may be partially responsible for the antiemetic effects of the lipid emulsion formulation of propofol. This prospective, randomized, and blinded study was designed to test this hypothesis in ambulatory surgical patients.

Materials and Methods

The protocol was approved by the University of Chicago Clinical Investigation Committee. Written informed consent was obtained from 60 unpremedi-

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Received from the Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois, and the Department of Anesthesia, University of Iowa, Iowa City, Iowa. Accepted for publication July 16, 1990.

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cated patients, ASA physical status I or II, scheduled for gynecologic laparoscopic surgery. Patients were randomized to receive either the 10% lipid solution in which propofol is emulsified (10% Intralipid, Kabi-Vitrum, Alameda, Calif.) or a control solution (5% dextrose in lactated Ringer's solution; D5LR). Before induction, all patients received 3 mg *d*-tubocurarine, 0.2 mg glycopyrrolate, and 1.5 μg/kg fentanyl. Four minutes later, anesthesia was induced with 4 mg/kg thiopental intravenously. Oral tracheal intubation was performed after succinylcholine injection (1.5 mg/kg). Anesthesia was maintained with enflurane (0.5%–2%) in 66% nitrous oxide (N_2O) and oxygen (O_2). Vecuronium bromide was used to maintain neuromuscular blockade. Twenty to twenty-five percent of the patient's muscle power was maintained as assessed with a peripheral nerve stimulator (8). Infusion of 10% Intralipid or the control solution was started at the same time as thiopental injection and continued for 20 min at the rate of 3 mL/min. This amount of Intralipid is about four times the amount a 70-kg patient would receive when anesthesia is induced with propofol. A syringe infusion pump (Medfusion Systems Inc., model 1001) was used for all infusions. After intubation, an orogastric suction tube was inserted with continuous suction applied until extubation. After completion of surgery, 0.6 mg glycopyrrolate and 3.0 mg neostigmine were administered for reversal of the neuromuscular blockade.

Blood pressure was measured (Dynamap, model 1846P) once per minute until the laparoscope was in place, and every 5 min thereafter. Electrocardiogram was monitored continuously. End-tidal carbon dioxide was measured continuously with a capnometer to maintain normoventilation in both groups. An additional 50 μg of fentanyl was administered immediately before placement of the laparoscopic trocar. Hemodynamic variables were maintained within 20% of awake measurements by adjusting the concentration of enflurane. Duration of anesthesia was reported as the time from the administration of thiopental until removal of the endotracheal tube. The times for extubation, spontaneous eye opening, and response to command were recorded from the time N_2O was discontinued.

The patient, the nurse who performed recovery room assessment, and the nurse who determined the need for antiemetic/pain medication were all blinded to the type of infusion (Intralipid versus control). Postoperative analgesia was provided with intravenous fentanyl (50 μg) or oral ibuprofen (800 mg) when the patient tolerated oral medication. In the postanesthesia care unit (PACU), the patients were observed constantly. Recordings of retching or vomiting were done at 15-min intervals. In addition, after every 15-min interval the patients were asked whether they had experienced any nausea during the last 15-min period. If any of these responses were positive, the patient was grouped as having emesis during that 15-min period. Severe nausea, retching, or vomiting lasting over two 15-min intervals was treated with 0.6 mg droperidol intravenously. The patients also completed visual analogue questionnaires about their subjective feeling of nausea and vomiting immediately before the procedure as well as just before their discharge. At discharge, the patients were asked to evaluate their overall amount of nausea and vomiting in the PACU. One end of the 100-mm-long visual analogue questionnaire was labeled as "none" and the other as "a lot." In the PACU, intermediate recovery was followed by recording the Aldrete score every 15 min until a score of 10 was reached (9). In addition, the times when the patients were able to sit, stand, walk, tolerate oral fluids, and urinate were recorded.

Statistical analysis for continuous data was performed using Student's *t*-test. Chi-square test with continuity correction was used for nonparametric variables. The required number of patients for each group was found to be 30 by a power analysis (10) predicated on the assumptions that two-tailed α = 0.05, and $\beta \leq 0.10$, and that the lipid emulsion would reduce nausea, retching, and vomiting by the same degree as would propofol (11).

Table 1. Demographic Characteristics

Group	Intralipid (n = 30)	Control (n = 30)
Age (yr)	29.6 ± 5.8	29.4 ± 7.3
Weight (kg)	72.2 ± 14.7	67.2 ± 12.8
Height (cm)	164 ± 8	162 ± 7
Duration of anesthesia (min)	56 ± 22	58 ± 37

Values are expressed as mean ± SD.

Results

A total of 60 ambulatory surgical patients, all of whom were undergoing gynecologic laparoscopies, were enrolled in the study. The groups were demographically similar in age, weight, ASA physical status, and duration of anesthesia (Table 1). Intraoperative anesthetic courses were similar in the two groups. There were no significant differences in the hemodynamic variables measured or the medications given.

Table 2. Recovery Characteristics

Time from turning N_2O off to	Intralipid (n = 30)	Control (n = 30)
Extubation (min)	6.2 ± 4.4	5.1 ± 4.5
Spontaneous eye opening (min)	6.7 ± 4.3	6.6 ± 5.2
Responds to command (min)	7.6 ± 4.9	7.9 ± 7.4
Orientation (min)	15.8 ± 9.9	14.1 ± 11.4
Aldrete score 10 (min)	24 ± 27	18 ± 19
Ability to sit (min)	100 ± 30	104 ± 42
Ability to stand (min)	133 ± 34	122 ± 42
Ability to tolerate oral fluids (min)	119 ± 68	99 ± 40
"Home-ready" (min)	182 ± 64	177 ± 69

Values are expressed as mean ± SD.

Table 3. Medications in the Postanesthesia Care Unit[a]

	Intralipid (n = 30)	Control (n = 30)
Fentanyl (50 μg)	7	10
Ibuprofen (800 mg)	19	17
Droperidol (0.625 mg)	5	4

[a] The numbers represent the number of patients in each group who received pain and/or antiemetic medication.

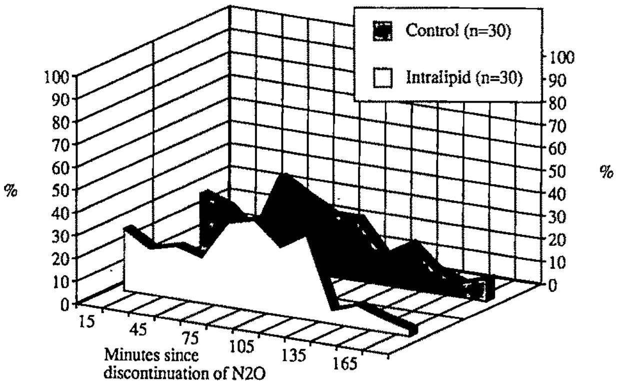

Figure 1. The percent of patients with nausea, retching, and/or vomiting at 15-min intervals in the PACU.

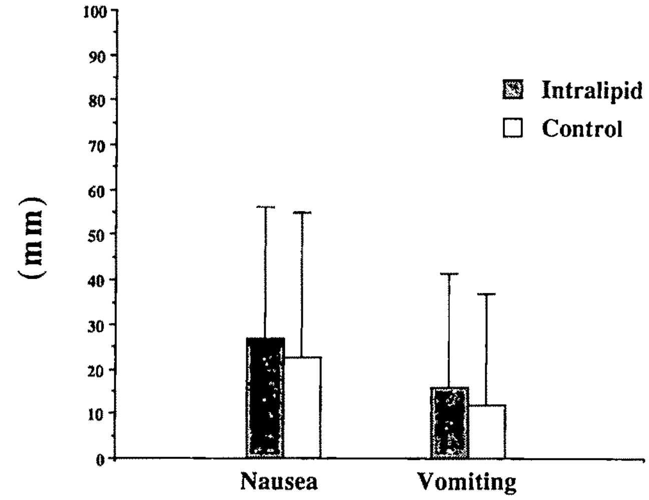

Figure 2. The degree of nausea and vomiting in the PACU as assessed by the patients using the visual analogue questionnaire.

Table 4. Frequency of Emesis

Group	Intralipid (n = 30)	Control (n = 30)
No emesis	8	9
Nausea	6	5
Retching	0	2
Vomiting	16	14

Early and intermediate recovery characteristics, as well as "home-readiness" were similar between the groups (Table 2). There were no significant differences in the amount of pain the patients experienced or pain medications used in the PACU (Table 3). No differences between the groups were found in the frequency of nausea, retching, and/or vomiting during any of the 15-min intervals as evaluated by the blinded nurse observer (Figure 1) or as quantified by the patient in the visual analogue questionnaire at discharge (Figure 2). Four patients in the control group and five patients in the lipid group received droperidol to control their emesis. The number of patients who did not have any nausea, retching, or vomiting during the PACU stay was similar in the two groups (Table 4).

Discussion

Emesis is one of the most unpleasant side effects after ambulatory surgery. The incidence and severity of postoperative nausea, retching, or vomiting when Cremophor EL was used as a solvent for propofol have not been specifically studied. No differences were found in the incidence of nausea or vomiting when alphadione or propofol general anesthesia was used in combination with regional anesthesia (3). One study reported a low incidence of nausea and vomiting after brief gynecologic procedures using Cremophor EL formulation of propofol, but no comparisons were made with other anesthetic agents (12). Methohexital and propofol were compared as induction agents in patients having minor gynecologic operations (13). These patients were visited within 24 h of surgery, and the occurrence of nausea and vomiting was recorded. Both groups had a low incidence of nausea and vomiting, but a slightly higher incidence was observed in the methohexital group. Finally, no differences were found in the incidence of vomiting or nausea in ambulatory patients who received thiopental/halothane/N_2O anesthesia compared with those who received propofol/N_2O anesthesia (14). The results of these earlier studies are difficult to analyze because the criteria for nausea, retching, or vomiting were sometimes poorly defined and the assessment of the incidence of nausea, retching, and vomiting was not the primary objective of the studies. However, one can conclude that no specific antiemetic effects were evident with the Cremophor EL formulation of propofol. This is in contrast to recent studies using the lipid emulsion formulation of propofol, in which a specific antiemetic effect has been reported (6).

Anesthesia is one of many factors (some others being surgical, metabolic, psychogenic, gastrointestinal) that may influence the incidence of postoperative nausea, retching, and vomiting. However, the anesthesiologist can influence the incidence of postoperative nausea and emesis with the choice of anesthetic agents. Recently, several studies have shown an incidence of postoperative nausea and vomiting in patients given propofol in lipid emulsion that is less than that with other anesthetic agents (5–7,11).

Studies of postoperative nausea and emesis usually group the patients into "yes" or "no" categories depending on the presence or absence of nausea, retching, or vomiting during the total time in the PACU. This type of categorizing does not reflect clinical outcome or the amount of care required by patients, i.e., a patient who vomits once is grouped together with a patient having prolonged nausea and/or emesis. In Figure 1 the groups are presented according to their emesis profile. The emesis profile is defined as the incidence of nausea, retching, and/or vomiting with respect to time periods in the PACU. It can be seen that there are no differences in the emesis profile between the groups.

The fat emulsion dose used in this study (60 mL) is about four times the amount a 70-kg patient would have received if anesthesia was induced with propofol. Earlier studies in ambulatory gynecologic patients where anesthesia was maintained with isoflurane and N_2O revealed that patients who received thiopental for the induction of anesthesia had more emesis than those who had received propofol for induction (15). Therefore, we assumed that this high dose should give a positive result if the fat emulsion had any clinically significant antiemetic effects.

To emphasize further our conclusion that the lipid emulsion is not the cause for the low frequency of nausea, retching, and vomiting associated with propofol anesthesia, the emesis profile of the propofol group from our previous study is included (Figure 3). The methods for assessing the frequency of nausea, retching, and vomiting, the type of surgery, and the patient characteristics in that study were similar to those in the present study. The emesis profile of the propofol group is clearly different from that of the groups in the present study.

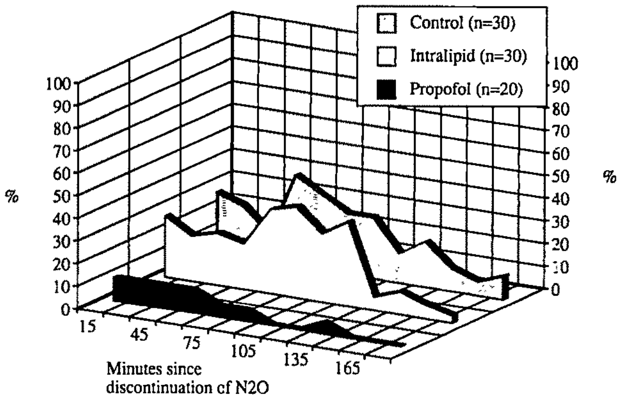

Figure 3. The percent of patients with nausea, retching, and/or vomiting at 15-min intervals in the PACU. The propofol group from a previous study (Reference 11) is shown for comparison.

This study demonstrated that Intralipid, the lipid in the emulsion formulation of propofol, does not possess significant antiemetic effects. Emesis is a reflex response of the vomiting center. Auditory and visual input, and stimuli from the autonomic nervous system, as well as other cortical stimuli and input from the chemoreceptor trigger zone, can provoke emesis. The mechanism of the low frequency of emesis after propofol anesthesia remains unknown. Propofol may stimulate the chemoreceptor trigger zone less than other anesthetics. The rapid clearance of propofol may also contribute to the apparently lower frequency of emesis postoperatively.

References

1. Doze V, Shafer A, White P. Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anesthesia. Anesthesiology 1988;69:63–71.
2. Kay B, Rolly G. ICI 35868, a new intravenous induction agent. Acta Anaesthesiol Belg 1977;28:303–16.
3. O'Callaghan AC, Normandale JP, Grundy EM, Lumley J, Morgan M. Continuous intravenous infusion of disoprofol (ICI 35868, Diprivan). Anaesthesia 1982;37:295–300.
4. Briggs LP, Clarke RSJ, Watkins J. An adverse reaction to the administration of disoprofol (Diprivan). Anaesthesia 1982;37:1099–101.
5. Gunawardene RD, White DC. Propofol and emesis. Anaesthesia 1988;43:65–7.
6. McCollum JSC, Milligan KR, Dundee JW. The antiemetic action of propofol. Anaesthesia 1988;43:239–40.

7. Korttila K, Östman PL, Faure E, Apfelbaum JL, Ekdawi M, Roizen MF. Randomized comparison of outcome after propofol-nitrous oxide or enflurane-nitrous oxide anaesthesia in operations of long duration. Can J Anaesth 1989;36:651–7.
8. Ali HH, Savarese JJ. Monitoring of neuromuscular junction. Anesthesiology 1976;45:216–22.
9. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970;49:924–34.
10. Dixon WJ, Massey FJ Jr. Introduction to statistical analysis. 4th ed. New York: McGraw-Hill, 1983.
11. Korttila K, Östman PL, Faure E, et al. Randomized comparison of recovery after propofol-nitrous oxide versus thiopentone-isoflurane-nitrous oxide anaesthesia in patients undergoing ambulatory surgery. Acta Anaesthesiol Scand (in press).
12. Briggs LP, Clarke RSJ, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropyl phenol as main agent for short procedures. Br J Anaesth 1981;53:1197–201.
13. Rutter DV, Morgan M, Lumley J, Owen R. ICI 35868 (diprivan): a new induction agent. Anaesthesia 1980;35:1188–92.
14. Jones DF. Recovery from day-case anaesthesia: comparison of a further four techniques including the use of the new induction agent diprivan. Br J Anaesth 1982;54:629–33.
15. Milligan KR, Howe JP, O'Toole JP, Dundee JW. Outpatient anesthesia: recovery after propofol, methohexital and thiopental (abstract). Anesth Analg 1987;66:S118.

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1990;71:541–4

A Comparison of Conductivity-Based Hematocrit Determinations With Conventional Laboratory Methods in Autologous Blood Transfusions

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McMAHON DJ, CARPENTER RL. A comparison of conductivity-based hematocrit determinations with conventional laboratory methods in autologous blood transfusions. Anesth Analg 1990;71:541–4.

An investigation was made of the accuracy of a portable hematocrit measurement device (Stat-Crit) on the infusate of an autologous blood transfusion system. Baseline hematocrit values were determined by three methods on in vivo blood samples of surgical patients immediately after the start of surgery, and again on the first product of the autologous blood retrieval system. At baseline, there were no significant differences in the values determined by the Stat-Crit (33.4% ± 6.2%, mean ± SD) and those determined by the microcentrifuge technique (33.8% ± 4.7%) or by the Coulter method (33.5% ± 4.5%) ($P = 0.9$). In contrast, hematocrit values determined on infusate samples by the Stat-Crit (36.6% ± 4.8%) were significantly lower than those determined by the microcentrifuge technique (51.2% ± 5.9%) or by the Coulter method (51.6% ± 5.8%) ($P = 0.0001$).

This study confirms close agreement of hematocrit values derived by the conductivity of whole blood in normal samples with those determined by conventional laboratory techniques, but indicates that this method will report falsely low readings in situations where plasma has been replaced by crystalloid, as in patients who have received large transfusions of processed autologous blood.

Key Words: BLOOD, HEMATOCRIT. TRANSFUSION, AUTOLOGOUS.

The proportion of packed cell volume in whole blood, or the hematocrit, has always been a useful factor in monitoring the hematologic status of patients undergoing major surgical procedures. Conventional laboratory methods for determining hematocrit are based on volumetric processing or individual cell detection. For almost 10 yr now, a compact device has been available (the Stat-Crit, Wampole Laboratories, Division of Carter-Wallace, Inc., Cranbury, N.J.) that determines hematocrit based on electrical conductivity. This device exploits the fact that erythrocytes offer a higher resistance to electrical conduction than plasma does. Previous studies have suggested a high correlation between hematocrit values determined by this method and those determined by standard laboratory techniques (1). However, we questioned whether this device would accurately measure hematocrit when blood plasma was diluted or replaced with crystalloid. One clinical situation where this occurs, to an extreme, is in the processing of blood in an autologous transfusion system. The typical blood retrieval and reinfusion technique involves the virtual replacement of blood plasma with saline. This replacement would be expected to alter the conductivity of the infusate and thus alter the hematocrit values returned by a conductivity-based device. This study was undertaken to compare the accuracy of the Stat-Crit with conventional techniques when applied to autologous infusate.

Methods

The population for this study consisted of patients undergoing elective surgical procedures for cardiothoracic surgery or total hip replacement. The study was approved by an investigational review board. For each patient, routine preoperative analyses performed within 24 h before surgery were checked to confirm that values for sodium, potassium, chloride, total protein, and white blood cell

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Received from the Department of Anesthesiology, Virginia Mason Medical Center, Seattle, Washington. Accepted for publication July 18, 1990.

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Table 1. Ranges of Whole Blood Values Needed for Use of Stat-Crit for Hematocrit Determinations

	Range of values
Serum electrolytes (mEq/L)	
Na$^+$	135–155
K$^+$	3.6–5.5
Cl$^+$	98–109
Plasma total protein (g/dL)	6.6–8.3
White cell count (cells/μL)	4,300–10,000

Table 2. Hematocrit Values Measured by the Three Techniques in Baseline (Control) Samples and in Processed Autologous Blood (Infusate) Samples

Sample	Centrifuge	Coulter STKR	Stat-Crit	*P*
Control	33.8 ± 4.7	33.5 ± 4.5	33.4 ± 6.2	0.9
Infusate	51.2 ± 5.9	51.6 ± 5.8	36.6 ± 4.8[a]	0.0001

[a] Different from centrifuge and STKR by the Scheffe *F*-test.

count fell within the ranges accepted as normal by the manufacturer of the Stat-Crit device (Table 1).

Within a total candidate population of 53 patients, 41 met the criteria for preoperative hematologic values defined above. Before use each day, the calibration of the Stat-Crit was confirmed using the manufacturer's recommended protocol.

In each patient, a 5-mL baseline sample of blood was taken from the arterial or venous catheter after the induction of anesthesia but before the processing of retrieved blood. Several drops of the sample were introduced into a disposable sample carrier, and the hematocrit was immediately determined in the Stat-Crit. The balance of the sample was drawn into a partially evacuated disposable tube containing 0.1 mL of tripotassium ethylenediaminetetraacetic acid anticoagulant. This sample was sent to the laboratory, where the hematocrit value was determined by two methods. In the microcentrifuge method, 0.1 mL of sample was drawn into two plain capillary tubes, sealed with clay, and spun in a microcentrifuge (Damon/IEC Corp model MB) at 10,000 to 15,000 *g* for 5 min. After removal from the centrifuge, the two capillary tubes were read for hematocrit in a microcapillary reader (IEC 2201); the two values agreed with each other within 2%. In the second method, the balance of the sample was drawn into the chamber of a Coulter Corp model STKR for analysis by the Coulter technique.

Blood lost during surgery was processed in the autologous transfusion system (Haemonetics Corp Cell-Saver model 3+) in which collected blood is pumped into a spinning centrifuge bowl and washed with physiologic saline, and the remaining concentrated red blood cells (RBCs) are transferred to a reservoir bag for subsequent reinfusion into the patient. A 5-mL sample of the first volume of processed blood was drawn from the infusate bag for analysis. As in the baseline sample, a hematocrit value was determined on site by the Stat-Crit, and the balance of the sample was sent to the laboratory for hematocrit determination by the two methods described above. The infusate sample was sent in a plain evacuated tube, without anticoagulant, because the infusate from the autologous transfusion system is devoid of clotting factors.

Laboratory determinations were conducted by a variety of medical technologists at various times of the day, and the two methods were performed in alternate sequences, so that human factors involving anticipated outcomes or irregularities in technique tended to be nullified. Patient identification number, surgical procedure, preoperative serum electrolyte levels, total plasma protein, white cell count, and all baseline and infusate hematocrit readings were recorded.

To establish the electrolyte levels in the autologous infusate, 10 randomly selected infusate samples were also analyzed in the laboratory for sodium, potassium, and chloride levels. These values were recorded and tabulated.

Correlations between hematocrit values determined by the three methods were assessed by simple linear regression. Differences between the hematocrit values determined by the three methods were assessed by analysis of variance. When significant differences were observed, they were identified by the Scheffe *F* test. $P < 0.05$ was considered to be statistically significant.

Results

There were no differences in the hematocrit values determined by the three methods in the baseline samples (Table 2). Hematocrit values measured on the baseline samples correlated well for all three methods, with $R^2 = 0.67$ with a slope of 1.08 for the regression of the centrifuge and Stat-Crit hematocrit values ($P = 0.0001$), $R^2 = 0.66$ with a slope of 1.12 for the regression of the STKR and Stat-Crit hematocrit values ($P = 0.0001$), and $R^2 = 0.97$ with a slope of 0.94 for the regression of the centrifuge and STKR hematocrit values ($P = 0.001$) (Figure 1).

Hematocrit values determined on infusate samples by the Stat-Crit were significantly lower than those determined by the other two methods (Table 2). The

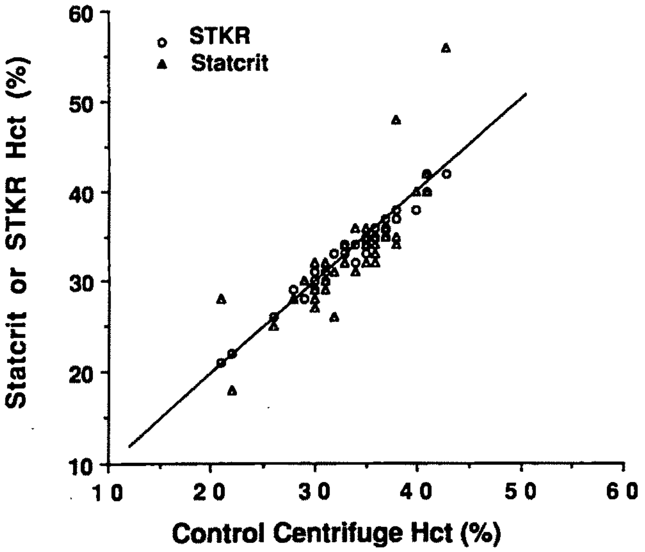

Figure 1. Correlation of Coulter STKR and Stat-Crit baseline hematocrit values with hematocrit values determined by centrifuge. The *solid line* represents the line of identity.

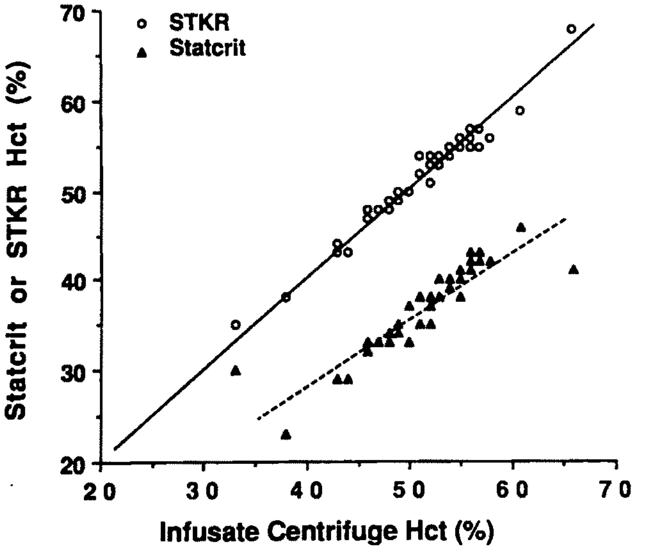

Figure 2. Correlation of Coulter STKR and Stat-Crit hematocrit values in autologous infusate with hematocrit values determined by centrifuge. The *dashed line* represents the regression line for the Stat-Crit values compared with those determined by the centrifuge. The *solid line* represents the line of identity.

differential between the averaged hematocrit value by laboratory methods and the Stat-Crit values was 14.8% ± 2.6% (mean ± SD). However, correlations between the values determined by the three methods remained excellent (Figure 2). $R^2 = 0.81$ with a slope of 0.72 for the regression of the centrifuge and Stat-Crit hematocrit values ($P = 0.0001$), $R^2 = 0.78$ with a slope of 0.73 for the regression of the STKR and Stat-Crit hematocrit values ($P = 0.0001$), and $R^2 = 0.96$ with a slope of 0.95 for the regression of the centrifuge and STKR hematocrit values ($P = 0.0001$).

The mean serum electrolyte levels in the 10 infusate samples were as follows: sodium, 162.8 ± 1.7 mEq/L; potassium, 4.8 ± 3.2 mEq/L; and chloride, 131.9 ± 2.1 mEq/L.

Discussion

In the original method of determining hematocrit described by Wintrobe, a relatively large sample of blood was spun at about 2000 *g* for 30 min (2). In the microcentrifuge technique, a pair of capillary tubes containing approximately 0.2 mL of blood are spun at 10,000 to 15,000 *g* for 5 min, and the proportion of column height is interpreted as the volume of packed erythrocytes by means of a calibrated visual reader. The method is subject to errors in cases of elevated white cell and platelet counts, trapped plasma, or poor technique. By the late 1970s, the microcentrifuge technique was virtually replaced in clinical laboratory practice by the Coulter method, which is based on the electrical characteristics of discrete cells (3). In the Coulter method, approximately 200 μL of sample is diluted, then aspirated through an aperture between two current-conducting electrodes. The passage of each RBC through the aperture creates a brief decrease in current due to the high impedance of RBCs. The number and amplitude of the current flow pulses is electronically interpreted in terms of RBC count and mean corpuscular volume, and the hematocrit is then calculated using these two factors. Each sample can be analyzed in less than 1 min.

The conductivity of RBCs was first investigated in 1929 by Stewart (4), but it was not until 1948 that the conductivity of whole blood in relation to RBCs was studied by Rosenthal and others (5,6). By the early 1960s, the first instruments were described for the determination of hematocrit based on the electrical conductivity of a blood sample (7–9). In the most recent refinement of the technique, as used in the Stat-Crit, approximately 0.1 mL of blood is introduced into the channel of a disposable plastic carrier, which is inserted into a retainer on the Stat-Crit. On insertion, two electrodes come into contact with the sample, and a microswitch is closed, starting the analysis. The sample is exposed to three separate high-frequency signals of about 0.3 s each, within a 5-s period. The averaged impedance, and thereby the conductivity, of the sample is measured, and the hematocrit (as well as the derived hemoglobin in g/dL) is displayed digitally.

Accuracy of the conductivity method of hematocrit determination depends on specific ranges of temperature, concentrations of electrolyte and total protein, and white cell count. The baseline samples in this study were within these ranges, and there was a high correlation of the values returned by the Stat-Crit with those obtained by both laboratory methods. In contrast, values determined by the Stat-Crit in infusate samples were significantly lower than those determined by the other two methods ($P = 0.0001$). Part of this variance may be explained by the high levels of sodium and chloride ions in the infusate of the autologous transfusion system. The increase in electrolyte concentration increases conductivity in the sample. Because plasma has a greater conductivity than RBCs, the increased total conductivity is interpreted by the Stat-Crit as a lower hematocrit. Literature accompanying the Stat-Crit suggests that an error of −1.3 in the hematocrit percentage should be expected for every 10 mEq/L increase in any of the three electrolytes (sodium, potassium, or chloride). The increased concentrations of sodium and chloride in the infusate should produce an error in the Stat-Crit readings of about −4 in the hematocrit percentage rather than the observed mean deviation of −14.8%. Because saline has an even greater conductivity than plasma, we suspect that the replacement of plasma with saline accounts for the additional error. The fact that total protein levels are virtually zero in the infusate is thus the most likely cause of this additional error.

The average volume of blood product reinfused in the population in this study was about 800 mL. But in protracted surgical procedures involving autotransfusion (extensive vascular revisions, transplants, or trauma), it is not uncommon for very large volumes (>2000 mL) of blood to be processed and reinfused. Progressive replacement of plasma with saline in these patients may produce a significant increase in conductivity of blood. Similarly, operations resulting in large blood losses that are replaced with crystalloid and packed RBCs could lead to substitution of crystalloid for plasma. We speculate that devices that derive hematocrit values by the conductivity method may give falsely low readings in these situations.

In conclusion, an investigation was made of the accuracy of a portable hematocrit measurement device (Stat-Crit) on the infusate of an autologous blood transfusion system. Baseline hematocrit values were obtained by three methods on in vivo blood samples of surgical patients immediately after the start of surgery and again on the first product of the autologous blood retrieval system. At baseline, there were no significant differences in the values determined by the Stat-Crit and those determined by the microcentrifuge technique or by the Coulter method. In contrast, hematocrit values determined on infusate samples by the Stat-Crit were significantly lower than those determined by the microcentrifuge technique or by the Coulter method.

References

1. Baris RR, Israel AL. Clinical evaluation of the Stat-Crit monitor. Proc Am Acad Cardiovasc Perfusion 1988;9:37–42.
2. Wintrobe M. Clinical hematology. Philadelphia: Lea & Febiger, 1971:367–9.
3. Coulter WH. High speed automatic blood cell counter and cell size analyzer. Proceedings of the National Electronics Conference, Chicago, Illinois. Hialeah, Fla.: Coulter Corp., 1956.
4. Stewart GN. The conductivity of erythrocytes compared with that of serum. Am J Physiol 1929;90:194–209.
5. Rosenthal RL, Tobias CW. Measurement of the electrical resistance of human blood. Use in coagulation studies. J Lab Clin Med 1948;33:1110–22.
6. Hirsch FG, Texter EC, Wood LA, Ballard WC, Horan FE, Wright IS. The electrical conductivity of blood. Relationship to erythrocyte concentration. Blood 1950;5:1017–35.
7. Okada RH, Schwan HP. An electrical method to determine hematocrits. IRE Transact Medical Elec 1960;7:188–92.
8. Kernan JA, Wurzel H, Okada R. New electronic method for measuring hematocrit: clinical evaluation. J Lab Clin Med 1961; 57:635–41.
9. Davis RE. An electronic instrument for measuring packed cell volume. Lab Pract 1966;15:1259–62.

Acute Progesterone Treatment Has No Effect on Bupivacaine-Induced Conduction Blockade in the Isolated Rabbit Vagus Nerve

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BADER AM, DATTA S, MOLLER RA, COVINO BG. Acute progesterone treatment has no effect on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1990;71:545–8.

Pregnancy decreases anesthetic requirements during regional anesthesia. Using an in vitro animal model, this study attempts to elucidate the mechanism of hormonal effects on nerve conduction in desheathed rabbit vagus nerve. The acute effects of progesterone administration on neural blockade induced by bupivacaine were investigated in terms of changes in compound action potentials of A, B, and C fibers. No change in baseline compound action potential was found after 30 min of perfusion of the nerve with progesterone. Exposure of the nerve to progesterone before exposure to bupivacaine did not significantly increase the degree of conduction blockade produced by bupivacaine, and a radioactive assay demonstrated that progesterone was taken up acutely by neural tissue over a 45-min measurement period. These results indicate that although progesterone was taken up in significant amounts by neural tissue, an acute exposure does not increase the sensitivity of the nerves to bupivacaine. Hence, the increased sensitivity of nerves to local anesthetics seen with pregnancy or with chronic progesterone treatment requires some period of time to occur. The mechanism is therefore unlikely to be a direct effect of progesterone on the cell membrane but may involve hormonal effects on protein synthesis.

Key Words: ANESTHETICS, LOCAL—bupivacaine. PREGNANCY, ANESTHETIC SENSITIVITY.

Pregnancy is associated with a decrease in anesthetic dose requirements. Pregnant women need approximately 25% less local anesthetic for epidural analgesia than nonpregnant women (1). Various theories have been proposed to explain this decrease in dose requirements. Distention of the epidural veins decreases the size of the epidural space and may increase spread of local anesthetics. Hormonal changes of pregnancy may alter nerve response to local anesthetics.

Isolated vagus nerves from pregnant rabbits or from rabbits chronically treated with progesterone are significantly more sensitive to bupivacaine-induced conduction blockade (2–4). The mechanism by which progesterone enhances the sensitivity of nerves to conduction blockade by local anesthetics is unclear. In previous in vitro studies, isolated nerves were chronically exposed to progesterone for periods ranging from 4 days to 4 wk. The present study attempts to determine whether acute exposure to progesterone is capable of producing changes in neural sensitivity. Determining the length of exposure required will help to define the actions of progesterone at the cellular level. The absence of an acute effect of progesterone on neural sensitivity to local anesthetic may imply that the mechanism does not involve a direct alteration in membrane permeability.

In the present study, isolated rabbit vagus nerves were acutely exposed to progesterone in the surrounding bathing medium for 30 min. The effect of acute progesterone exposure alone on conduction blockade was measured. The effect of acute pretreatment with progesterone on conduction blockade produced by bupivacaine was also evaluated. Finally, the amount of radioactive progesterone taken up by the neural tissue during this period of acute exposure was determined.

Received from the Department of Anesthesia, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts. Accepted for publication July 23, 1990.

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Methods

Animals were housed in an animal-care facility approved by Harvard Medical School and the National Institutes of Health, and were treated in accordance with the Harvard Medical Area Guidelines for animal care and use of laboratory animals. Vagus nerves were obtained from New Zealand white rabbits supplied by Milbrook Farms of New England and weighing 4.5–5.5 kg. Animals were anesthetized with intravenous thiamylal (1.5 mg/kg) before being killed by intravenous air embolus. The vagus nerves were rapidly removed, desheathed, and stored at room temperature (22°C) in HEPES-Liley solution containing 136.8 mM NaCl, 5.0 mM KCl, 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2$, and 11.0 mM dextrose, and buffered by the addition of 3.0 mM *N*-2-hydroxyethylpiperazine-*N*′-2-ethane sulfonic acid (HEPES). The pH was adjusted to 7.35–7.40 by the addition of 0.1 N NaOH. The progesterone solution was prepared by suspending progesterone in absolute alcohol, evaporating the alcohol with a warming bath, and resuspending the progesterone in HEPES-Liley to obtain a concentration of 200 ng/mL.

The desheathed nerves were transferred to a plexiglass stimulation chamber, and an electrophysiologic method involving sucrose gap was used (5). One end of the nerve was stimulated by bipolar extracellular electrodes (Ag/AgCl) in small pools (~50 μL each) containing control buffer solution and isolated from the recording pools by petroleum jelly. An 8-mm length of the nerve was exposed to drugs in the same solution (~300 μL) containing one of the Ag/AgCl recording electrodes; the other electrode rested in a HEPES solution that bathed the other "intracellular" end of the nerve. These two recording zones are separated by a "sucrose-gap" consisting of a hollow cylinder of 3-mm diameter, which intersects the nerve to perfuse it with the insulating, nonionic sucrose (isotonic at 0.25 M). Because of the removal of extracellular ions in the sucrose-gap by continuous perfusion of the nonelectrolyte (2–3 mL/min), the action potentials cannot propagate through this region. The potential between the two electrodes is proportional to the true transmembrane potentials, averaged for the different fibers. Nerves were stimulated using surface platinum electrodes with a Grass stimulator and Grass Stimulus Isolation Unit. Stimulus intensities were adjusted to obtain the maximum compound action potential (CAP) on a Tektroniks model 5113 storage oscilloscope. Measurements of the CAP were made from photographs of the images displayed on the storage oscilloscope. The A, B, and C fibers were identified by their respective conduction velocities. Compound action potentials were recorded every 5 min during the observation periods. At the end of each set of experiments, at least 80%–90% recovery of control CAP was required to ensure that any observed conduction blockade was not secondary to nerve damage.

Three sets of experiments were performed. The first set of experiments determined whether baseline CAP changed after acute exposure to progesterone alone (n = 10 vagus nerves). After stabilization, half of the nerves were perfused with HEPES-Liley for 30 min and half were perfused with progesterone in HEPES-Liley for 30 min with CAP measured at 5-min intervals.

The second set of experiments looked at the effect of acute pretreatment with progesterone on the conduction blockade produced by bupivacaine in two groups of nerves. The first group of 14 nerves was exposed to progesterone for 30 min, and the second group of 14 nerves was exposed to HEPES-Liley for the same period of time. Seven nerves in each group were then treated with 0.025 mM bupivacaine and seven nerves with 0.05 mM bupivacaine for a period of 30 min. The compound action potential was recorded at 5-min intervals throughout these periods. After exposure to bupivacaine, all nerves were washed in HEPES-Liley until 80%–90% recovery of baseline CAP was obtained.

The third group of experiments determined the amount of progesterone taken up by neural tissue in this study. Five nerves were placed in test tubes with 1 mL of solution containing tritium-labeled progesterone. The nerves were rinsed thoroughly in HEPES-Liley and were disintegrated overnight in 1 mL of 1 N KOH in scintillation vials in a 40°C oven. The amount of radioactive progesterone taken up after 5, 15, 30, and 45 min was measured in a scintillation chamber.

At the end of the first two sets of experiments, the peak CAPs for A, B, and C fibers were recorded and compared with baseline values. Results were expressed as indicated in the figures, either as mean CAP amplitude or as percent reduction in CAP amplitude achieved at the end of the 30-min exposure periods. Results for the second and third sets of experiments are expressed as mean ± standard error. Linear regression analysis and analysis of variance were used where appropriate to determine differences between groups. Statistical significance was assumed with P values less than 0.05.

Results

The first set of experiments showed no change in baseline CAP after acute exposure to progesterone

(Figure 1). Each graph describes the results of a separate fiber type. For each fiber type, the amplitude of CAP at 0, 15, and 30 min is illustrated. No significant changes in CAP amplitude appeared over the 30-min measurement period in any of the fiber types in the two groups. There were no significant differences in CAP between the nerves infused with HEPES-Liley and the nerves infused with progesterone at any point measured during the infusion period.

The second set of experiments showed that acute pretreatment with progesterone did not significantly increase the amount of conduction blockade produced by 0.25 or 0.5 mM bupivacaine. Figure 2 illustrates data using the higher concentration of bupivacaine. For each fiber type, the degree of depression of baseline CAP is illustrated after exposure first to HEPES-Liley and then to bupivacaine (solid bars), and after exposure first to progesterone and then to bupivacaine (dotted bars). There were no significant differences in the amount of depression of baseline CAP by bupivacaine after acute exposure to either HEPES-Liley or progesterone.

The third set of experiments showed that during the period of acute exposure progesterone was taken up by neural tissue (Figure 3). The amount of progesterone contained in the neural tissue continued to increase over the 45-min measurement period.

Discussion

Both anatomic and hormonal effects may be responsible for the wider dermatomal spread of anesthesia after epidural administration of local anesthetic solutions to pregnant patients (1). Chronic exposure to progesterone alters local anesthetic sensitivity to nerve fibers (2–4). Changes in the connective tissue or in the sensitivity of the nerve membrane have been proposed as explanations. Results from the present study indicate that although progesterone is taken up in significant amounts by neural tissue after acute exposure, the acute exposure to progesterone does not increase the sensitivity of the nerves to bupivacaine. Previous studies from our laboratory have shown that intact vagus nerves have an increased sensitivity to bupivacaine after chronic exposure to progesterone, perhaps resulting from a cellular alteration affecting sensitivity to local anesthetics. Acute exposure does not produce the same alteration.

In our previous experiments, the connective tissue sheath was not removed from the nerves before drug exposure. The current study is the first from our laboratory that utilizes desheathed nerves. This prep-

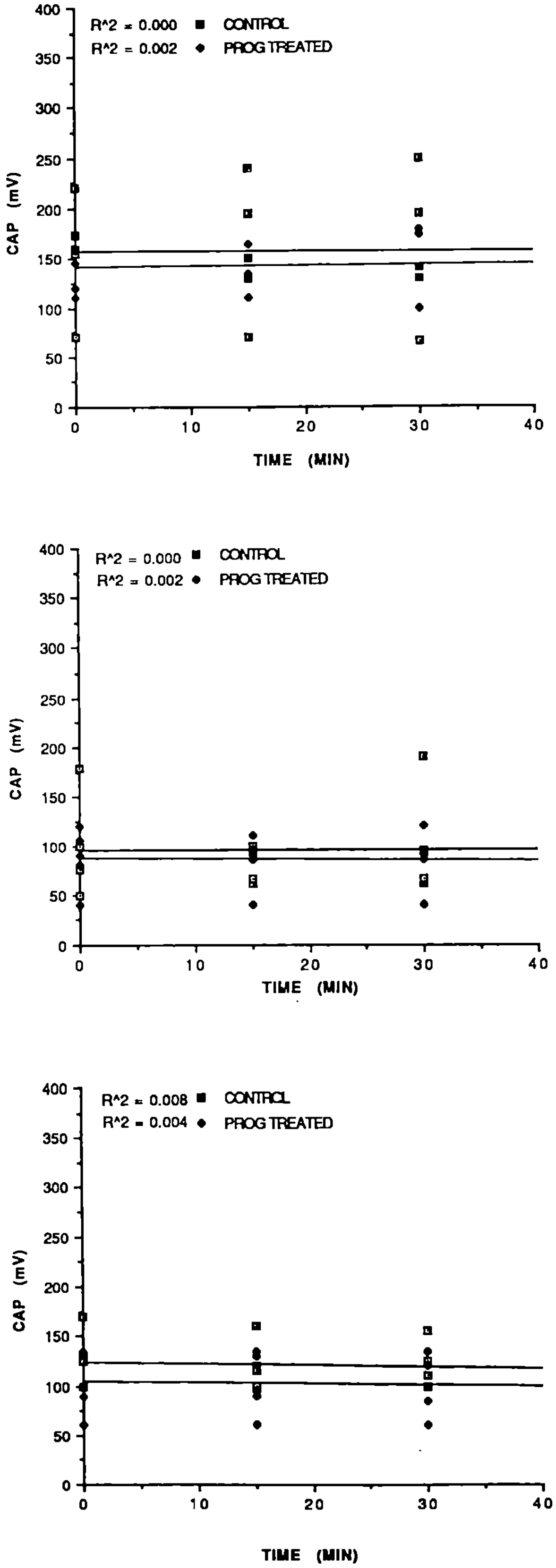

Figure 1. Compound action potential amplitude after acute exposure to either HEPES-Liley or prcgesterone. *Top*, A fibers; *middle*, B fibers; *bottom*, C fibers.

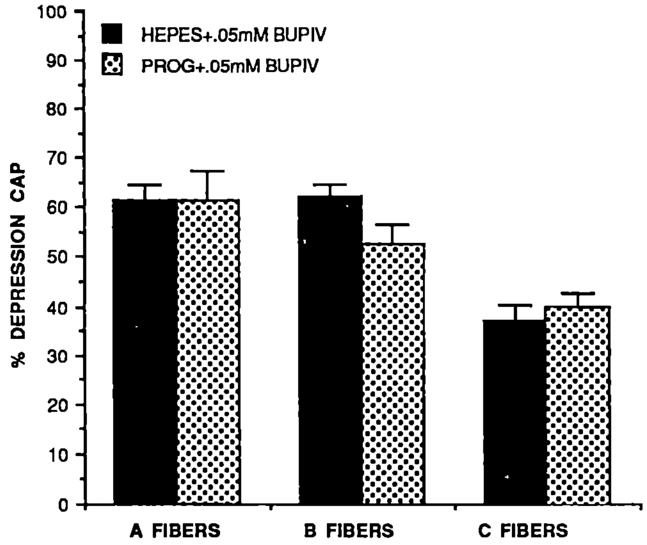

Figure 2. Percent depression of CAP by 0.5 mM bupivacaine after acute exposure to either HEPES-Liley or bupivacaine.

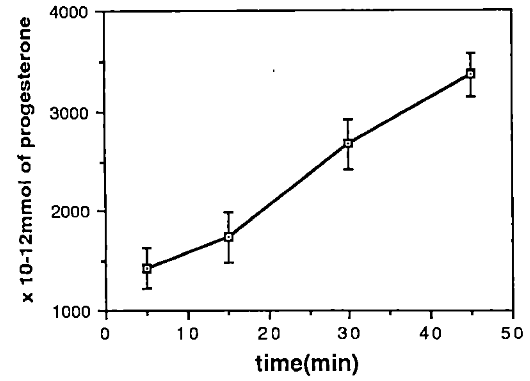

Figure 3. Amount of radioactive progesterone taken up by neural tissue during acute exposure.

aration eliminates the influence of drug diffusion across the connective tissue sheath as a factor and therefore gives a more accurate representation of drug effect on the nerve membrane itself. This measurement is representative of the average resting potential and the true monophasic action potentials from the different fiber types. In contrast to the "extracellular chamber" used with sheathed nerves, the sucrose-gap measures the behavior of the nerve membrane directly exposed to drug. Progesterone and estrogen are known to alter the permeability of the intercellular connective tissue matrix, which might facilitate diffusion of local anesthetics across the nerve sheath (6). The finding that acute exposure in the desheathed nerve does not increase local anesthetic-induced conduction blockade would seem to eliminate acute hormonal effect on the connective tissue matrix as an etiology. In previous studies, a significant difference in the CAP produced by bupivacaine was found between the group chronically treated with progesterone and the control groups once the nerve preparation stabilized and a steady-state block was achieved. The fact that this difference existed during the steady-state block would also seem to indicate that progesterone effects on the connective tissue matrix are not solely responsible for the differences seen.

The concentration of progesterone to which nerves were exposed in this experiment was much higher than that expected in the pregnant animal (6 ng/mL) and was chosen because it was similar to concentrations measured in the animals chronically treated with progesterone in our previous studies. These supramaximal concentrations are used to ensure that any progesterone effects will be apparent and will not be dependent on concentration.

The mechanism by which progesterone alters local anesthetic sensitivity is unclear. Progesterone is known to alter protein synthesis (7), and possibly may influence proteins that affect membrane sensitivity. Chronic exposure to progesterone may result in the formation of metabolites that interact with the neural sodium channels so that the addition of bupivacaine results in the blockade of a greater number of functional channels. Further studies will attempt to elucidate these mechanisms better.

References

1. Bromage PR. Continuous lumbar epidural analgesia for obstetrics. Can Med Assoc J 1961;85:1136–40.
2. Datta S, Lambert D, Gregus J, Gissen AJ, Covino BG. Differential sensitivities of mammalian nerve fibers during pregnancy. Anesth Analg 1983;62:1070–2.
3. Flanagan HL, Datta S, Moller RA, Covino BG. Effect of exogenously administered progesterone on susceptibility of rabbit vagus nerve to bupivacaine. Anesthesiology 1988;69:A676.
4. Flanagan HL, Datta S, Lambert DH, Gissen AJ, Covino BG. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1987;66:123–6.
5. Stampfli R. A new method for measuring membrane potentials with external electrodes. Experientia 1954;12:580–9.
6. Gianetti A, Cerimele D. Effect of steroid hormones on the matrix of the dermis of the rat. In: Balazs EA, ed. Chemistry and molecular biology of the intercellular matrix. Volume III. London: Academic Press, 1970:1821–7.
7. Liu YC, Greengard P. Regulation of steroid hormones of phosphorylation of specific protein common to several target organs. Proc Natl Acad Sci 1976;73:568–72.

ANESTH ANALG 1990;71:549–53

Baseline Activated Coagulation Time Should Be Measured After Surgical Incision

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GRAVLEE GP, WHITAKER CL, MARK LJ, ROGERS AT, ROYSTER RL, HARRISON GA. Baseline activated coagulation time should be measured after surgical incision. Anesth Analg 1990;71:549–53.

The activated coagulation time (ACT) is widely used to guide heparin and protamine dosing during cardiac surgery. A common protocol involves establishing a baseline ACT before administering heparin, then using this ACT as a target value for assessing the adequacy of heparin neutralization after cardiopulmonary bypass. Results vary in previous comparisons of baseline ACT to postprotamine ACT, with some showing postprotamine ACT significantly below baseline values. The present study examined ACTs at three possible baseline intervals in 68 patients at two institutions: (a) before anesthetic induction; (b) after anesthetic induction; and (c) after sternotomy. Baseline ACT decreased significantly with anesthesia and surgery. The poststernotomy baseline ACT best matched the postprotamine ACT. It appears likely that surgery induces a thromboplastic response that decreases ACT. Establishing baseline ACT before anesthetic induction would predispose to false diagnoses of adequate protamine neutralization after cardiopulmonary bypass, because ACT is relatively insensitive to low concentrations of unneutralized heparin. Baseline ACTs should therefore be measured after surgical incision.

Key Words: BLOOD, CLOTTING—activated coagulation time (ACT).

Since Bull et al. introduced heparin monitoring to cardiac surgery in 1975, use of the activated coagulation time (ACT) has become widespread (1,2). Activated coagulation time is a whole-blood clotting time that uses a contact surface activant to facilitate clotting. This activant, commonly diatomaceous earth, reduces blood clot formation time within a test tube from approximately 4–6 min to approximately 1.5–2.5 min, depending on the specific methods used. The clinical utility of ACT in cardiac and vascular procedures stems from simplicity, bedside availability, sensitivity to heparin-induced anticoagulation, and the fairly rapid availability of results. Activated coagulation time primarily tests the intrinsic plasma coagulation cascade, but the results can be influenced by platelet abnormalities. Whole-blood heparin concentration can be measured directly, but the ACT appears more useful because it measures the anticoagulant effect of heparin, and patients vary widely in their sensitivity to heparin-induced anticoagulation.

Activated coagulation time management protocols commonly involve establishing a baseline (or control) ACT before administering heparin for cardiopulmonary bypass (CPB). This value then serves as a starting point for a heparin versus ACT dose-response curve and as a target value for heparin neutralization with protamine. Bull et al. obtained baseline ACTs from patients either the night before surgery or upon arrival in the operating room (1,2). Several subsequent studies have evaluated ACT-based heparin management, but none have reported the time of baseline ACT measurements more specifically than "before heparin" (3–8).

One recent study reported postprotamine ACTs significantly below ACTs measured before anesthetic induction (9), which initiated debate about possible explanations for this observation (10,11). We reasoned that anesthesia and surgery might alter the baseline ACT, and tested this hypothesis by measuring ACT at three intervals before anticoagulation for CPB.

Presented in part at the April 1989 annual meeting of the Society of Cardiovascular Anesthesiologists, Seattle, Washington.

Received from the Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina, and the Department of Anaesthesia, St. Vincent's Hospital/University of New South Wales, Darlinghurst, New South Wales, Australia. Accepted for publication July 25, 1990.

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Methods

After obtaining approval from human research practices committees at both institutions, 68 patients were studied, excluding patients receiving heparin or warfarin within 5 days of surgery. Patients were grouped by institution: group 1 consisted of 48 patients (35 men, 13 women; mean age, 60 ± 9 [SD] yr) undergoing cardiac surgery requiring CPB (39 coronary artery bypass grafts [CABG], eight valve replacements, one combined CABG/valve) at Wake Forest University Medical Center. Activated coagulation time samples were taken from a radial artery catheter (20-gauge Teflon) separated from the blood sampling site by 15 cm of high-pressure tubing (sampling dead space <1.0 mL). Before aspirating ACT samples, a 5-mL sample was withdrawn to clear the heparin flush solution (12,13). Protamine doses were determined by an automated protamine titration algorithm (HemoTec Inc., Englewood, Colo.).

Group 2 included 20 patients (15 men, five women; mean age, 63 ± 7 yr) undergoing similar cardiac procedures (17 CABG, two valve replacements, one combined CABG/valve) at St. Vincent's Hospital. In this group, ACT samples were taken via a radial artery catheter (20-gauge Teflon), approximately 100 cm of high-pressure tubing (sampling dead space <3.0 mL), and a three-way stopcock after withdrawing 20 mL to clear the heparin flush solution (12,13). For this group, an initial intravenous protamine dose of 2 mg/kg was administered, followed in 5 min by an ACT measurement. After this an additional 50 mg of protamine was given, followed by another ACT measurement. Subsequent 50-mg protamine increments were given only if ACT remained higher than the lowest pre-CPB ACT and decreased ≥12 s after the first 50-mg supplement.

In both groups, ACT was measured at four intervals: before anesthetic induction, 5–10 min after completing anesthetic induction and endotracheal intubation (before surgical incision), 5 min after sternotomy, and 5 min after completing protamine infusion into the right atrium. In group 2 patients the postprotamine ACT was defined as the lowest ACT obtained during the in vivo protamine titration described above. Activated coagulation times were measured using 2.0 mL of whole blood placed in Celite-activated tubes through an 18-gauge needle. The tubes were then placed in a Hemochron 400 or 800 automated ACT device (International Technidyne, Metuchen, N.J.).

Activated coagulation times at each of the different sampling times were compared with one another by Holm's sequentially rejective paired two-tailed *t*-test (14), with $P < 0.05$ considered to be statistically significant.

Table 1. Activated Coagulation Time Values During Cardiac Surgery

Time of determination	Group 1	Group 2
Preinduction	141 ± 11	150 ± 20
Postinduction	136 ± 15^{a}	140 ± 25^{a}
Sternotomy	130 ± 12^{a,b}	120 ± 23^{a,b}
Protamine	130 ± 11^{a,b}	129 ± 19^{a,b}

Activated coagulation time given in seconds.

[a] $P < 0.05$, compared with preinduction values.

[b] $P < 0.05$, compared with postinduction values.

Results

Table 1 shows the ACT results at different times by group. Within both groups, all paired ACT comparisons differed significantly except for the poststernotomy versus postprotamine comparison. The standard deviations overlap considerably, largely reflecting ACT variation between patients. Figure 1 shows a frequency distribution of the change in ACT from the preinduction value for the two study groups combined, displaying similar patterns toward ACT reduction that are slightly more pronounced at the sternotomy and protamine measurements than at the postinduction ones. Figure 2 depicts the frequency and size of ACT reductions between the preinduction and poststernotomy sampling times with consideration of the expected variability of the test (9). Combining the two groups, ACT decreased in 84% of patients in the interval between those two blood samples. Assuming a coefficient of variation of 4% for ACT under control conditions (9), 75% of patients experienced ACT reduction ≥1 standard deviation (SD) of the preinduction value, and 47% showed reductions ≥2 SD. Thus, the statistical significance of the paired ACT comparisons within each group results from the consistent direction of change within individual patients, rather than from diminution of the group mean ACT values.

Discussion

The level of baseline ACT usually decreases over the period spanning anesthetic induction and surgical incision. Is this information clinically helpful? Table 2 shows ACTs from three patients, with patient A representing the most common pattern, which is consistent with previous reports comparing only pre-

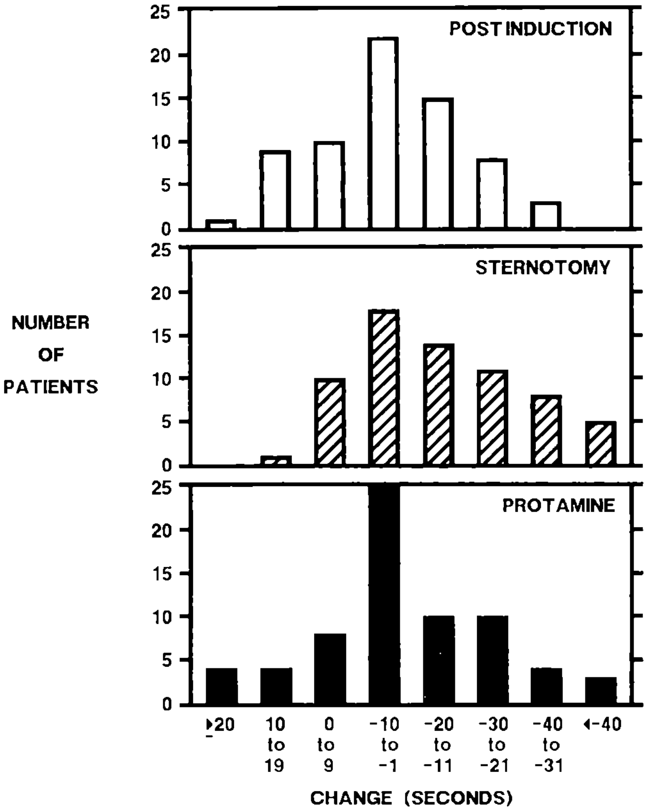

Figure 1. Frequency distribution of the change in ACT from preinduction to the other three measurement times. A negative value represents an ACT decrease from preinduction to the other measurement period shown on the graph.

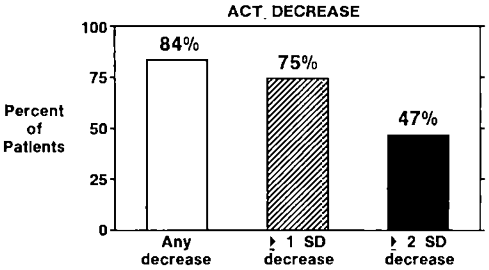

Figure 2. Percent of patients whose ACT decreased from the preinduction value to the sternotomy value.

induction and postprotamine ACTs (9,11). Patient B shows marked ACT reduction over the prebypass period and an initial postprotamine ACT approximating the preinduction value. An additional 50-mg increment of protamine then brought the ACT much closer to the poststernotomy value. Without the sternotomy ACT, one might have assumed that the initial postprotamine ACT of 137 s represented complete heparin neutralization. An additional 50 mg of protamine improved hemostasis and reduced the ACT to 86 s. Patient C shows the least common pattern. An additional 50-mg protamine dose was administered after obtaining the postprotamine ACT of 151 s, assuming that this value represented incomplete heparin neutralization. Rather than reducing the ACT toward 123 s (poststernotomy baseline), supplemental protamine increased ACT to 161 s. This suggests that heparin was already either fully neutralized or overneutralized, because excessive protamine increases ACT (15,16). Alternatively, reductions in plasma coagulation factors or platelet function could have increased ACT independent of heparin or protamine effects. If hemostasis had been inadequate in patient C, the comparison of sternotomy and postprotamine ACTs would have suggested the need for clotting factors, platelets, or possibly desmopressin. Diagnostic efforts could have then progressed toward a coagulation profile or thromboelastography.

Table 2. Activated Coagulation Times in Three Patients

Time of determination	Patient A	Patient B	Patient C
Preinduction	149	144	147
Postinduction	128	107	142
Sternotomy	122	79	123
Protamine 1[a]	127	137	151
Protamine 2[b]		86	161

Activated coagulation time given in seconds.
[a] Activated coagulation times after first dose of protamine.
[b] Activated coagulation times after an additional 50 mg of protamine.

Activated coagulation time functions well as a monitor of CPB anticoagulation because it is relatively insensitive to heparin. At the level of anticoagulation needed for cardiac surgery, laboratory tests more sensitive to heparin (e.g., thrombin time, activated partial thromboplastin time) become markedly prolonged or unclottable (17). Although relative insensitivity to heparin favors the ACT for monitoring anticoagulation during CPB, it diminishes its ability to diagnose incomplete heparin neutralization after CPB adequately (6,18,19). Clinically significant concentrations of unneutralized heparin may exist even if ACT returns to baseline after protamine. Because anesthesia and surgery decrease ACT, obtaining the baseline value before surgical incision might provide false reassurance later about the adequacy of heparin neutralization. Because excessive protamine can increase both ACT and postoperative bleeding (15,20,21), it appears desirable to establish baseline ACT as accurately as possible. Consequently, to maximize the post-CPB diagnostic utility of a relatively imprecise test (9) that lacks sensitivity to low concentrations of heparin (6,18,19), pre-CPB baseline ACT is best obtained after surgical incision.

Some imprecision exists in the protamine dosing methods used in both groups, and this may contribute to postprotamine ACT variability. Clinically significant protamine dosing errors would tend to elevate the ACT regardless of whether too much or too little protamine were given (15). This might account for some of the preinduction to postprotamine ACT increases shown in Figure 1. However, the similarity of the overall frequency distributions shown in Figure 1 and the similar postprotamine ACT values in groups 1 and 2 (using different methods for protamine dose determination) suggest that inappropriate protamine dosing did not bias the postprotamine ACT values.

Six previous reports provide both prebypass and postprotamine ACT values (5,6,9–11,22). Only two of these clearly obtained the prebypass ACT before inducing anesthesia, and both found postprotamine ACT values significantly below preinduction ones (9,11). Jobes et al. (10) presented some similar findings, but the difference was smaller and less consistent. Kamath and Fozard showed nearly equal ACTs before CPB and after protamine (5); other investigators found postprotamine ACTs higher than pre-CPB values (6,22). Some of these differences might be explained by different baseline ACT sampling times, most of which were unspecified (5,6,10,22). In the two studies showing higher ACTs after protamine than before CPB (6,22), either insufficient or excessive protamine would provide possible explanations (15,16).

The mechanism for ACT reduction over the pre-CPB period cannot be elucidated from the present study, but a thromboplastic response to surgical incision seems likely. Other studies have shown biochemical evidence of plasma coagulation activation during surgery (21,23,24), but did not compare preoperative and intraoperative (before heparin) clotting times. Tuman et al. showed thromboelastographic evidence of a hypercoagulable state during surgery (25). Bode and Eick demonstrated in vitro that lysed platelets reduced the ACT toward normal after fresh blood was anticoagulated with heparin, possibly owing to platelet factor IV release or a procoagulant effect of platelet membranes (26). We speculate that other clotting times such as the activated partial thromboplastin time, prothrombin time, and template (Ivy) bleeding time might also decrease after surgical incision. The ACT decrease after anesthetic induction is more difficult to explain. Preinduction ACT was taken immediately after inserting the radial artery catheter, after which either a pulmonary artery catheter (group 1) or a triple-lumen central venous catheter (group 2) was inserted. Perhaps the presence of indwelling catheters stimulates intravascular coagulation. Intravenous anesthetics or the stress response to laryngoscopy and intubation might also play a role.

In summary, anesthesia and surgery decrease ACT, thus resetting the baseline value. The poststernotomy ACT closely approximates postprotamine ACT. It seems likely that this would also occur after surgical incision and before sternotomy. Therefore, to simplify baseline ACT sampling, we recommend determining baseline ACT in cardiac surgical patients at some point between surgical incision and heparin administration.

References

1. Bull BS, Korpman RA, Huse WM, Briggs BD. Heparin therapy during extracorporeal circulation. I. Problems inherent in existing heparin protocols. J Thorac Cardiovasc Surg 1975;69:674–84.
2. Bull BS, Huse WM, Brauer FS, Korpman RA. Heparin therapy during extracorporeal circulation. II. The use of a dose-response curve to individualize heparin and protamine dosage. J Thorac Cardiovasc Surg 1975;69:685–9.
3. Babka R, Colby C, El-Etr A, Pifarre R. Monitoring of intraoperative heparinization and blood loss following cardiopulmonary bypass surgery. J Thorac Cardiovasc Surg 1977;73:780–2.
4. Verska JJ. Control of heparinization by activated clotting time during bypass with improved postoperative hemostasis. Ann Thorac Surg 1977;24:170–3.
5. Kamath BS, Fozard JR. Control of heparinization during cardiopulmonary bypass. Experience with the activated clotting time method. Anaesthesia 1980;35:250–6.
6. Dauchot PJ, Berzina-Moettus L, Rabinovitch A, Ankeney JL. Activated coagulation and activated partial thromboplastin times in assessment and reversal of heparin-induced anticoagulation for cardiopulmonary bypass. Anesth Analg 1983;62: 710–9.
7. Lefemine AA, Lewis M. Activated clotting time for control of anticoagulation during surgery. Am Surg 1985;51:274–8.
8. Preiss DU, Schmidt-Bleibtreu H, Berguson P, Metz G. Blood transfusion requirements in coronary artery surgery with and without the activated clotting time (ACT) technique. Klin Wochenschr 1985;63:252–6.
9. Gravlee GP, Case LD, Angert KC, Rogers AT, Miller GS. Variability of the activated coagulation time. Anesth Analg 1988;67:469–72.
10. Jobes DR, Campbell FW, Ellison N. Limit(ation)s for ACT. Anesth Analg 1989;69:142–3.
11. Gravlee GP. Limit(ation)s for ACT (letter). Anesth Analg 1989;69:143–4.
12. Palermo LM, Andrews RW, Ellison N. Avoidance of heparin contamination in coagulation studies drawn from indwelling lines. Anesth Analg 1980;59:222–4.
13. Clapham MC, Willis N, Mapleson WW. Minimum volume of discard for valid blood sampling from indwelling arterial cannulae. Br J Anaesth 1987;59:232–5.
14. Holm S. A simple sequentially rejective multiple test procedure. Scand J Statistics 1979;6:65–70.
15. Dutton DA, Hothersall AP, McLaren AD, Taylor KM, Turner MA. Protamine titration after cardiopulmonary bypass. Anaesthesia 1983;38:264–8.

16. Kresowik TF, Wakefield TW, Fessler RD II, Stanley JC. Anticoagulant effects of protamine sulfate in a canine model. J Surg Res 1988;45:8–14.

17. Schriever HG, Epstein SE, Mintz MD. Statistical correlation and heparin sensitivity of activated partial thromboplastin time, whole blood coagulation time, and an automated coagulation time. Am J Clin Pathol 1973;60:323–9.

18. Hooper TL, Conroy J, McArdie B, et al. The use of the Hemochron in assessment of heparin reversal after cardiopulmonary bypass. Perfusion 1988;3:295–300.

19. Esposito RA, Culliford AT, Colvin SB, Thomas SJ, Lackner H, Spencer FC. The role of the activated clotting time in heparin administration and neutralization for cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983;85:174–85.

20. Guffin AV, Dunbar RW, Kaplan JA, Bland JW. Successful use of a reduced dose of protamine after cardiopulmonary bypass. Anesth Analg 1976;55:110–3.

21. Gravlee GP, Haddon WS, Rothberger HK, et al. Heparin dosing and monitoring for cardiopulmonary bypass: a comparison of techniques with measurement of subclinical plasma coagulation. J Thorac Cardiovasc Surg 1990;99:518–27.

22. Ottesen S, Stormorken H, Hatteland K. The value of activated coagulation time in monitoring heparin therapy during extracorporeal circulation. Scand J Thorac Cardiovasc Surg 1984;18:123–8.

23. Davies GC, Sobel M, Salzman EW. Elevated plasma fibrinopeptide A and thromboxane B2 levels during cardiopulmonary bypass. Circulation 1980;61:808–14.

24. Mammen EF, Koets MH, Washington BC, et al. Hemostasis changes during cardiopulmonary bypass surgery. Semin Thromb Hemost 1985;11:281–92.

25. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Effects of progressive blood loss on coagulation as measured by thromboelastography. Anesth Analg 1987;66:856–63.

26. Bode AP, Eick L. Lysed platelets shorten the activated coagulation time of heparinized blood. Am J Clin Pathol 1989;91:430–4.

Clinical Reports

Treatment of Refractory Seizures in Massive Isoniazid Overdose

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Key Words: ANTIBIOTICS, ISONIAZID—convulsions. BRAIN, CONVULSIONS—isoniazid.

Acute massive isoniazid overdose is relatively uncommon but potentially life-threatening (1). In the setting of accidental or intentional overdose, seizures are a frequent manifestation of isoniazid neurotoxicity (2). The consulting anesthesiologist may become involved when seizures prove refractory to the administration of standard anticonvulsants and pyridoxine, the conventional isoniazid antidote (3). In this report, we describe the management of such a case of isoniazid-induced seizures; we also discuss the specificity and efficacy of thiopental as a treatment for refractory isoniazid-induced seizures in a patient with arterial hypotension.

Case Report

A 25-yr-old man presented to the emergency room at the University of Missouri Hospital about 1.75 h after ingesting approximately 18 g of isoniazid in a suicide attempt.

He was awake and talking upon arrival, but moments later he abruptly began having generalized convulsions. Face-mask ventilation with 100% O_2 was begun, and an intravenous catheter was inserted. Physical examination was remarkable for ongoing generalized convulsions in an apparently otherwise healthy young, approximately 70-kg man. He had tachycardia with a stable blood pressure within the normal range. No respiratory effort was apparent (Table 1).

Diazepam and pyridoxine were administered intravenously in sequential injections. Each bolus resulted in a brief interruption of the seizures, which would then recur. The entire available pharmacy supply of pyridoxine (12 g) was administered in this manner. One gram of phenobarbital was also given intravenously without effect.

After approximately 25 min of unsuccessful anticonvulsant therapy, an anesthesiologist was consulted. Physical examination at that time revealed a diaphoretic, unconscious, convulsing man with a stable blood pressure but increasing tachycardia. Initial measurements of arterial blood gas tensions showed a profound combined metabolic and respiratory acidosis. The electrocardiogram showed marked sinus tachycardia with an intraventricular conduction delay.

Meanwhile, the trachea was orally intubated and a nasogastric tube was passed for gastric lavage. To correct his metabolic acidosis, sodium bicarbonate was administered intravenously. To correct the respiratory component, the patient was mechanically hyperventilated after an intravenous bolus of pancuronium bromide. The electroencephalogram (EEG) was monitored using a two-channel, compressed spectral array tracing, which revealed slowing of electrical activity over both cerebral hemispheres (Figure 1), consistent with ongoing seizures.

As a 2.5% thiopental infusion was being prepared, the patient rapidly developed hypotension and profound tachycardia. A radial artery catheter was inserted and the hypotension corrected with an intravenous bolus of normal saline and an infusion of phenylephrine. An infusion of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine was also begun. Meanwhile, thiopental was given initially in 12.5-mg IV boluses, then as a continuous infusion at an approximate rate of 2.5

Received from the Department of Anesthesiology, University of Missouri-Columbia School of Medicine, Columbia, Missouri. Accepted for publication June 21, 1990.

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Table 1. Chronology of Therapeutic Intervention From Onset of Isoniazid-Induced Seizures to Recovery

Approximate time after ingestion (hours:min)	Event	Blood pressure (mm Hg)	Pulse (beats/min)	Arterial blood gas values			Therapy
				pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	
1:45	Patient arrived in emergency room	—	—	—	—	—	—
1:50	Onset of convulsions	140/88	122	6.95	32	123	Initiate anticonvulsant therapy: IV valium (40 mg); IV phenobarbital (1 g); IV pyridoxine (12 g). Face-mask ventilation; increase Fio_2 to 1.0.
2:15	Anesthesiologist consulted	131/80	142	6.65	97.8	443	IV bicarbonate (88 mEq); IV pancuronium (10 mg). EEG monitoring; tracheal intubation; mechanical hyperventilation; decrease Fio_2 to 0.50.
2:30	Patient developed hypotension	65/35	158	7.12	45.8	489	Resuscitation with IV normal saline bolus; IV phenylephrine (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$); IV bicarbonate (88 mEq). Begin IV dopamine infusion (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$); radial artery catheter placed; decrease Fio_2 to 0.40.
2:40	Begin thiopental infusion	98/42	132	—	—	—	Infuse a total dose of 3.5 g.
2:55	Convulsions stopped, hemodynamics stabilized	118/53	112	7.44	32.2	273	Taper off phenylephrine; taper off thiopental; continue dopamine; central venous catheter placed for hemodialysis.
14:00	Dialysis completed	135/70	87	7.37	42.1	243	Observe in intensive care unit; initiate ventilatory weaning; stop dopamine infusion.
24:00	Patient awake, alert, appropriate	132/64	77	7.45	35.7	167.9	Extubate patient; plan for discharge from hospital within 48 h.

$mg \cdot kg^{-1} \cdot min^{-1}$. Faint generalized muscle twitching was seen as the infusion was begun, confirming the presence of ongoing seizures seen on the EEG.

After a total thiopental dose of approximately 3.5 g, the physical examination and EEG (Figure 2) demonstrated that seizure activity had abated and the infusion of thiopental was stopped. The vital signs stabilized and the phenylephrine infusion was also tapered off. Emergency hemodialysis was then initiated. The dopamine infusion was discontinued upon completion of hemodialysis.

His subsequent recovery was prompt and uneventful. Levels of serum electrolytes and arterial blood gas tensions after hemodialysis were in the normal range. His serum creatinine level was normal throughout his hospital stay, and levels of liver function tests remained normal except for a mild, transient elevation of the alkaline phosphatase and serum aspartate aminotransferase. Within 36 h of admission the patient was awake, extubated, conversant and suffering only from short-term memory loss. He was subsequently referred to a mental health center for treatment of depression.

Discussion

Isoniazid-induced seizures are believed to result from the impaired production of the inhibitory neurotransmitter, γ-amino butyric acid (GABA) (2,4). Isoniazid interrupts GABA production by inhibiting the active form of pyridoxine, a necessary cofactor in the enzymatic pathway for GABA synthesis (5). The result is lowered levels of GABA in the brain with subsequent heightened central nervous system (CNS) excitability and seizures (6).

Pyridoxine replacement replenishes GABA levels and restores the balance of excitatory and inhibitory neurotransmitters in the CNS. As such, pyridoxine is central to the treatment of isoniazid-induced seizures. A gram-for-gram replacement, if available, based upon the estimated isoniazid dose is recommended (3). As much as 52 g has been given to an adult without apparent ill effects. The maximum safe dose of pyridoxine in humans is unknown, but in dogs a dose of 1 g/kg proved fatal in several cases (7).

The efficacy of pyridoxine and anticonvulsants is improved by the addition of alkali to correct meta-

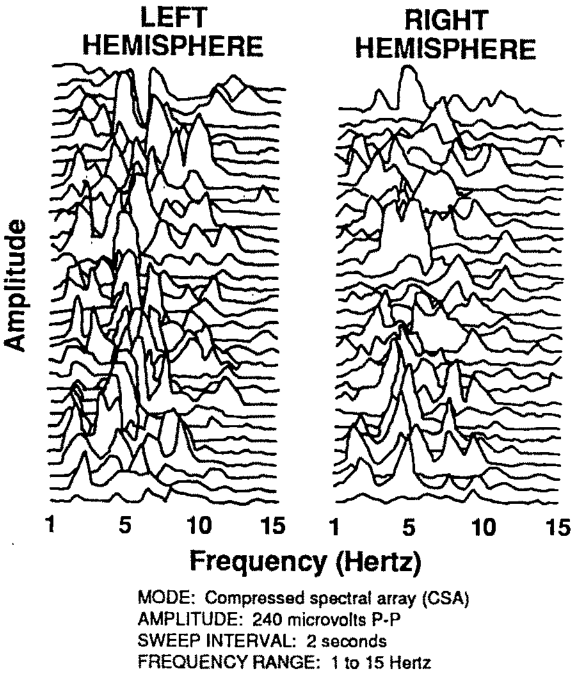
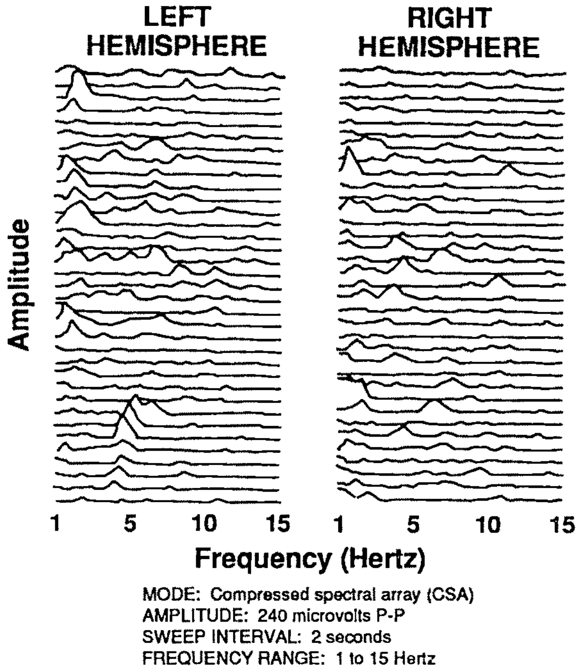

LEFT HEMISPHERE
RIGHT HEMISPHERE
Amplitude
1
5
10
15
1
5
10
15
Frequency (Hertz)
MODE: Compressed spectral array (CSA)
AMPLITUDE: 240 microvolts P-P
SWEEP INTERVAL: 2 seconds
FREQUENCY RANGE: 1 to 15 Hertz

Figure 1. Compressed spectral array tracing showing low-frequency, high-voltage seizure activity.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Frequency (Hertz)
MODE: Compressed spectral array (CSA)
AMPLITUDE: 240 microvolts P-P
SWEEP INTERVAL: 2 seconds
FREQUENCY RANGE: 1 to 15 Hertz

Figure 2. Compressed spectral array tracing showing barbiturate-induced slowing and resolution of seizures.

bolic acidosis (8,9), which may be profound (10,11), as in the present case. Caution must be used, however; because lactate accumulation from seizure activity is the primary cause of acidosis (12), the cessation of seizures results in spontaneous resolution of acidosis, and bicarbonate administration may cause potentially harmful overcorrection (13).

Hemoperfusion (14) or hemodialysis (15) may be helpful to remove the systemic isoniazid and improve acid/base status if forced diuresis proves inadequate. The physical properties of isoniazid—a small, water-soluble molecule that is poorly protein-bound and that has a small volume of distribution—suggest that it would be efficiently removed from the circulation by dialysis. Anecdotal reports seem to support this conclusion (14). In contrast, the physical properties of thiopental—a large, lipid-soluble molecule that is extensively protein-bound and that has a large volume of distribution—make it unlikely to be efficiently removed by dialysis. We predict, therefore, that thiopental is protective against recurrent seizures in a patient who is receiving a dialytic procedure as therapy for isoniazid overdosage.

The transient elevation of plasma levels of hepatic enzymes as seen in this patient is known to occur after massive isoniazid overdose (16,17), and is apparently without sequelae.

Compressed spectral array monitoring proved very useful in the present case. Although it is not intended as a diagnostic device, the compressed spectral array monitor does provide baseline EEG data consistent with a known clinical situation, and it is a means for monitoring change. In our case, the monitor was easily transported and quickly applied to the patient. It provided a baseline tracing in a paralyzed patient who was known to have ongoing grand mal seizures (Figure 1), and it provided a clinical endpoint consistent with successful barbiturate therapy (Figure 2).

The anticonvulsant mechanism of thiopental is incompletely understood. Barbiturates in general have a complex action in the CNS and almost certainly have multiple sites of action. The anticonvulsant and sedating properties of barbiturates (and also of benzodiazepines) probably arise at least in part from their activity at the postsynaptic GABA receptor-ionophore complex (18). γ-Amino butyric acid acts at this receptor site to enhance membrane permeability to chloride ions, thus hyperpolarizing the membrane. Recent evidence suggests that other neurotransmitters may also act on this same ionophore complex in opposition to GABA (19). The barbiturates bind to an adjacent allosteric site (20) and prolong the GABA-induced membrane permeability to chloride (21,22). In addition, the barbiturates may act through an independent mechanism to inhibit the release of excitatory neurotransmitters (23,24). The sum of these effects is CNS depression by a mechanism that is directly opposed to the GABA-inhibitory effects of isoniazid.

Although any ultra-short-acting barbiturate presumably can be considered a specific GABA agonist, thiopental is the most extensively studied in this regard. Methohexital, although less of a cardiovascular depressant, has been implicated as a cause of psychomotor seizures in children (25). We chose thiopental because of our familiarity with the drug. The volatile anesthetics, although probably effective, are not specific for GABA and are limited for practical reasons in duration of use and portability. A typical dosage of diazepam was also ineffective in terminating the seizures in our patient. Benzodiazepines in general are less easily titrated and slower in onset than the ultra-short-acting barbiturates.

If a patient has intractable seizures, or if there is a limited pyridoxine supply, our experience in this case is that a thiopental infusion, if used cautiously, can be a safe and efficacious adjunct to the standard anticonvulsant therapy associated with isoniazid overdosage—even in the presence of arterial hypotension. Promptness of therapy is essential to assure optimal neurologic outcome, and in our patient seizure activity was terminated within 15 min of initiating the thiopental infusion. No adverse side effects occurred. We conclude that thiopental is an appropriate and readily available drug for the prompt treatment of isoniazid-induced seizures that prove refractory to the available conventional modalities of treatment.

References

1. Brown CV. Acute isoniazid poisoning. Am Rev Respir Dis 1972;105:206–16.
2. Sievers ML, Herrier RN. Treatment of active isoniazid toxicity. Am J Hosp Pharm 1975;32:202–6.
3. Wason S, Lacouture PG, Lovejoy FH. Single high-dose pyridoxine treatment for isoniazid overdose. JAMA 1981;246: 1102–4.
4. Wood JD, Peesker SJ. A correlation between changes in GABA metabolism and isonicotinic acid hydrazide induced seizures. Brain Res 1972;45:489–98.
5. Wood JD, Peesker SJ. The effect on GABA metabolism in brain of isonicotinic acid hydrazide and pyridoxine as a function of time after administration. J Neurochem 1972;19:1527–37.
6. Holtz D, Palm D. Pharmaceutical aspects of vitamin B_6. Pharmacol Rev 1964;16:113–78.
7. Unna IC. Studies of the toxicity and pharmacology of vitamin B_6 (2-methyl-3-hydroxy-4, 5-*bis*-[hydroxymethyl]-pyridine). J Pharmacol Exp Ther 1940;70:400–7.
8. Terman DS, Teitelbaum DT. Isoniazid self-poisoning. Neurology 1970;20:299–304.
9. Konigshausen T, Altrogge G, Hein D, et al. Hemodialysis and hemoperfusion in the treatment of most severe INH-poisoning. Vet Hum Toxicol 1979;21(Suppl):12–5.
10. Dixon AC, Shikuma L, Duvauchelle DA, Rappaport DS, Nakamura JW. Isoniazid overdose: a case report. Hawaii Med J 1988;47:558–9.
11. Hankins DG, Saxena K, Faville RJ, Warren BJ. Profound acidosis caused by isoniazid ingestion. Am J Emerg Med 1987;5:165–6.
12. Sitprija V, Holmes JH. Isoniazid intoxication. Am Rev Respir Dis 1964;90:248–51.
13. Yarbrough BE, Wood JP. Isoniazid overdose treated with high-dose pyridoxine. Ann Emerg Med 1983;12:303–5.
14. Leibenwitz H, Krevolin L, Schwartz A. Hemoperfusion treatment of massive isoniazid overdose. Delaware Med J 1989;61: 71–3.
15. Giacona N. Hemodialysis therapy of INH overdose. Drugdex System Drug Consult DC3183, 1982.
16. Spalding CT, Buss WC. Toxic overdose of isoniazid, rifampicin and ethambutol. Eur J Clin Pharmacol 1986;30:381–2.
17. Blanchard PD, Yao JD, McAlpine DE, Hurt RD. Isoniazid overdose in the Cambodian population of Olmstead County, Minnesota. JAMA 1986;256:3131–3.
18. Nicoll RA, Eccles JC, Oshima T, et al. Prolongation of hippocampal inhibitory postsynaptic potentials by barbiturates. Nature 1975;258:625.
19. Pfeiffer-Linn C, Glantz RM. Acetylcholine and GABA mediate opposing actions on neuronal chloride channels in crayfish. Science 1989;245:1249–51.
20. Higashi H, Nishi S. Effect of barbiturates on the GABA receptor of cat primary afferent neurons. J Physiol (Lond) 1982;332:299–314.
21. Study RE, Barker JL. Diazepam and (-)pentobarbital. Fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. Proc Natl Acad Sci USA 1981;78:7180–4.
22. Barker SL, Ranson BR. Pentobarbitone pharmacology of mammalian central neurones grown in tissue culture. J Physiol (Lond) 1980;280:355–72.
23. Richards CD, Smaje JC. Anaesthetics depress the sensitivity of cortical neurones to L-glutamate. Br J Pharmacol 1976;58: 347–57.
24. Smaje JC. General anaesthetics and the acetyl-choline sensitivity of cortical neurones. Br J Pharmacol 1976;58:359–66.
25. Rockoff MA, Goudsouzian NG. Seizures induced by methohexital. Anesthesiology 1981;54:333.

1990;71:558–60

Anesthetic Management of Cerebral Aneurysm Resection in a Patient With Idiopathic Hypertrophic Subaortic Stenosis

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Key Words: HEART, IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS. ANESTHESIA, NEUROSURGICAL—cerebral aneurysm.

Idiopathic hypertrophic subaortic stenosis (IHSS), also known as hypertrophic and obstructive cardiomyopathy, is characterized by asymmetric hypertrophy of the interventricular septum, causing intermittent obstruction of the left ventricular outflow tract. Patients may be asymptomatic or may present with angina, congestive heart failure, arrhythmias, or sudden death. Outflow tract obstruction is worsened by decreases in either preload or afterload or by increases in cardiac contractility. Anesthetic management of IHSS is therefore based on agents and techniques that limit these changes in cardiovascular function.

The anesthetic management of cerebral aneurysm resection involves volume restriction and diuresis to decrease intracranial pressure and to improve surgical exposure. Induced hypotension is often required to reduce the risk of rupture during aneurysm resection. Thus, the management of IHSS and cerebral aneurysm resection presents conflicting therapeutic objectives.

We describe our management of a patient with documented symptomatic IHSS who presented for cerebral aneurysm clipping after an acute subarachnoid hemorrhage.

Report of a Case

A 75-yr-old woman presented with a severe headache and confusion. Cerebral angiography revealed a subarachnoid hemorrhage. A neuroradiologic examination by computed axial tomography showed an aneurysm of the anterior communicating artery. Her past medical history was significant for IHSS diagnosed 1 yr earlier, during an episode of severe chest pain. Cardiac evaluation at that time was negative for a myocardial infarction. Left ventricular ejection fraction was 89% by radionuclide ventriculography. Echocardiography was nondiagnostic for IHSS; however, cardiac catheterization documented a left ventricle to aorta gradient of 0 mm Hg at rest and 35 mm Hg after amyl nitrate. This gradient established the diagnosis of IHSS. Coronary artery anatomy was normal. She was subsequently medicated with verapamil (40 mg tid).

The patient had no cardiac symptoms at the time of admission. Her height and weight were 4 ft 10 in and 46 kg. Admission blood pressure was 130/92 mm Hg with a heart rate of 66 beats/min. There were no murmurs, gallops, or abnormal pulmonary sounds heard on chest auscultation. Therapy with nimodipine (60 mg every 4 h), phenytoin (100 mg tid), decadron (10 mg qid), and ranitidine (50 mg tid) was begun by the neurosurgical service. Preoperative blood counts and serum electrolyte levels were within normal limits. An electrocardiogram showed sinus bradycardia without other abnormality. The patient received verapamil, nimodipine, phenytoin, decadron, and ranitidine, and was then transported to the operating room. An intraarterial catheter was inserted in the left radial artery and a pulmonary artery catheter in the right subclavian vein.

Preinduction vital signs included blood pressure, 160/100 mm Hg; heart rate, 68 beats/min; pulmonary artery pressures, 28/15 mm Hg; and cardiac output, 3.3 L/min. Anesthesia was induced with 350 mg thiopental, 500 μg fentanyl, and 5 mg pancuronium intravenously, and ventilation was controlled before uneventful tracheal intubation. Induction was well tolerated hemodynamically. Five boluses of phenylephrine, 100 μg intravenously each, were administered over the next 30 min for mild hypotension (systolic blood pressure, 90–100 mm Hg) during

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Received from the Department of Anesthesiology, Yale-New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication July 11, 1990.

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placement of a lumbar cerebrospinal fluid (CSF) drain. Anesthesia was maintained with air/oxygen and 0.5%–1.0% isoflurane. Mannitol (1 g/kg IV) was given at the time of skin incision with no subsequent hemodynamic changes. An esmolol intravenous bolus (0.5 mg/kg) and intravenous infusion (0.05 $mg \cdot kg^{-1} \cdot min^{-1}$) were also started. Before aneurysm resection, hypotension was induced to a mean arterial pressure of 70 mm Hg for 60 min. This was accomplished by giving an additional esmolol intravenous bolus (0.25 mg/kg) and increasing the intravenous infusion (0.06–0.10 $mg \cdot kg^{-1} \cdot min^{-1}$). The inspired isoflurane concentration was also increased to 2.0%. Pulmonary artery systolic and diastolic pressures ranged from 28 to 32 mm Hg and from 14 to 20 mm Hg, respectively with cardiac outputs of 2.5–3.0 L/min. The aneurysm was successfully clipped. There were no electrocardiographic changes and no heart murmurs noted throughout the operation.

The trachea was extubated upon emergence from anesthesia before the patient left the operating room. Vital signs remained stable in the postoperative period, and no neurologic deficits were noted. Serial postoperative electrocardiogram showed no new changes; plasma concentrations of cardiac isoenzymes were within normal limits.

Discussion

Anesthetic management of noncardiac surgery in patients with IHSS has been described for obstetrics, general surgery, and orthopedics (2–7). It has not been reported for cerebral aneurysmectomy to our knowledge.

General principles of management of IHSS include maintenance of adequate preload and afterload, and avoidance of tachycardia and increased contractility. Mainstays of therapy include β-blockers and calcium channel blockers. These classes of drugs have both negative inotropic and chronotropic effects to decrease outflow tract obstruction. They may also improve diastolic filling of the ventricle. Transesophageal echocardiography is very useful as a guide to therapy in the patient with IHSS. Positioning and manipulation of the echo probe, however, may be difficult in the neurosurgical patient in whom there is limited access to the head and neck area. At the time of surgery, a transesophageal echocardiography machine was unavailable for our use.

Several conflicting issues of operative management had to be resolved in this case. These included choice of anesthetic agent, management of volume status, and management of induced hypotension.

Halothane and enflurane, with their negative inotropic and chronotropic characteristics, are commonly recommended for anesthetic maintenance in IHSS. Although isoflurane decreases systemic vascular resistance and may cause reflex tachycardia, it appears in many studies (8,9) to have more favorable attributes than either halothane or enflurane with regard to intracranial pressure. Isoflurane decreases the cerebral metabolic rate for oxygen and causes the least increase in cerebral blood flow when compared with halothane and enflurane (especially with simultaneous hyperventilation). In addition, isoflurane does not significantly affect CSF production or reabsorption. Enflurane may provoke seizure activity when combined with hyperventilation, and in addition may increase CSF production and decrease CSF reabsorption (10–12). We therefore elected to use isoflurane. Because of the duration of the operative procedure and the use of fentanyl during induction, pancuronium was used rather than vecuronium. It was injected slowly during the induction of anesthesia to minimize its vagolytic effect on the cardiac conduction system. Esmolol infusion was utilized to prevent the tachycardia commonly associated with isoflurane.

Normovolemia to mild hypovolemia is usually maintained in our patients with elevated intracranial pressure. Furthermore, osmotic diuresis with mannitol is employed to decrease brain size. Hypovolemia, which causes reduction of left ventricular preload, can aggravate outflow tract obstruction in IHSS. By monitoring pulmonary artery pressures and cardiac output, and with the utilization of β blockade to control heart rate, we were able to accomplish both fluid restriction and osmotic diuresis without hemodynamic sequelae.

A moderate level of induced hypotension was induced at the time of aneurysm clipping. Commonly used drugs, such as nitroprusside or nitroglycerin, which increase venous capacitance and decrease systemic vascular resistance, are relatively contraindicated in IHSS. We accomplished adequate hypotension by increasing the esmolol infusion with concomitant increase of the concentration of isoflurane. No adverse effects were noted and the surgeon was quite satisfied with the operative field.

In summary, we present our anesthetic management of cerebral aneurysm resection in a patient with IHSS. Invasive monitoring allowed utilization of techniques (e.g., osmotic diuresis and induced hypotension) that facilitated the surgery, but that otherwise are contraindicated in this disease. Short-acting β-blockade with esmolol proved very beneficial in both accomplishing these goals and possibly preventing

Letters to the Editor

Hearing Loss After Spinal Anesthesia

Key Words: ANESTHETIC TECHNIQUES, SPINAL—hearing. EAR, HEARING—spinal anesthesia.

To the Editor:

I read with interest the article by Fog et al. (1) on hearing loss after spinal anesthesia. In their discussion section, the authors state that the etiology of vestibulocochlear disturbances after spinal anesthesia is not clear, but that it is possible that the decrease in cerebrospinal fluid pressure that follows dural puncture may be transmitted through the cochlear aqueduct to the inner ear, resulting in an endolymphatic hydrops. It is difficult to understand how the decrease in cerebrospinal fluid pressure causes an endolymphatic hydrops. There is an anatomic communication between cochlea and subarachnoid space through the cochlear canal, and the perilymph that occupies the perilymphatic space in the cochlea resembles cerebrospinal fluid closely in its composition. Hughson (2) demonstrated that a decrease in cerebrospinal fluid pressure is associated with a decrease in intralabyrinthine pressure followed by a functional inability of an ear to transmit the sound. Hence, a decrease in intralabyrinthine pressure is most likely the cause of the hearing loss after spinal anesthesia.

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References

1. Fog J, Wang LP, Sunberg A, Mucchiano C. Hearing loss after spinal anesthesia is related to needle size. Anesth Analg 1990;70:517–22.
2. Hughson W. A note on the relationship of cerebrospinal and intralabyrinthine pressure. Am J Physiol 1932;101:396–407.

In Response:

We are greatly indebted to Dr. Lee for his kind interest. It is well known that the perilymph in the inner ear communicates freely with the cerebrospinal fluid, and it has been demonstrated that changes in cerebrospinal fluid pressure may cause similar changes in perilymphatic pressure (1). The endolymph, on the other hand, is contained in a much more closed compartment and communicates with the endolymphatic sac through the endolymphatic duct.

A decrease in cerebrospinal fluid volume may reduce the perilymphatic pressure, and, as the endolymphatic pressure equilibrates slowly compared to the perilymphatic pressure, an endolymphatic hydrops may result.

Thus we agree with Dr. Lee that the decrease in intralabyrinthine pressure most likely causes the transient hearing loss that may follow spinal anaesthesia.

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Reference

1. Carlborg B. Transmission of cerebrospinal fluid pressure via the cochlear aqueduct and the endolymphatic sac. Am J Otolaryngol 1983;4:273–82.

Bupivacaine-Induced Cardiac Arrest

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—brachial plexus block. ANESTHETICS, LOCAL—bupivacaine.

To the Editor:

The views expressed in Dr. Boba's letter (1) commenting on a case report by Long et al. of severe cardiac arrest and arrhythmia after a probable inadvertent intravascular injection during an axillary nerve block (2) deserve comment. There is no doubt in our minds that a brachial plexus block, either by supraclavicular or axillary approach, is indicated in emergencies like the one described (3,4), but we question why, in the case report that Dr. Boba is commenting upon, instead of using a continuous technique (5–7), the axillary block was done with a single injection of lidocaine, a medium-lasting local anesthetic, for a surgical procedure that on the optimistic side would take at least several hours to complete.

We also question whether Dr. Boba's argument that the patient would not be comfortable because of the long

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duration of the surgery can be accepted nowadays. An effective block, with a pain-free patient, makes it simple to use sedation. The intravenous injection of small amounts of midazolam (1–2 mg) or flunitrazepam (200–300 μg) reinforced, if needed, with fentanyl for analgesia (25–50 μg) is enough to produce a tranquil, quiet subject who will remember very little if anything about his or her operation (8).

The Sellick maneuver cannot guarantee a safe intubation in a patient with a full stomach. Regional anesthesia is safer. Besides, with a catheter in place, the analgesia and sympathetic block can be extended for days. This also would provide better vascular perfusion of the arm and so improve the chances of success for any grafts done in the hand or fingers. Postoperative pain can also be controlled without any systemic hypnoanalgesics, avoiding in this manner their side effects.

We would have managed the anesthesia for a case like this basically in the same way that Long et al. did, with the difference that our axillary block would have been a continuous one and that the patient would have been sedated with midazolam. Sleep and amnesia would have been present, and stress would have been avoided. We do not believe that the reported complication would have occurred if the procedure had been carried out in such a way.

On the other hand, Long and colleagues are to be commended for saving the patient by using the extraordinary recourse of extracorporeal circulation when all the other means failed. As far as we know, this is the first time in the history of anesthesia that this method has been used to treat apparently irreversible cardiac arrest and fibrillation.

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References

1. Boba A. Bupivacaine-induced cardiac arrest (letter). Anesth Analg 1990; 70:464–5.
2. Long WB, Rosenblum S, Grady IP. Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass. Anesth Analg 1989;69:403–6.
3. Fortuna A. Bloqueios anestésicos. Rev Bras Anestesiol 1963;13:226–62.
4. Fortuna A. Bloqueios anestésicos. Rev Bras Anestesiol 1963;13:326–51.
5. Winnie A. Plexus anesthesia. 1st ed. Philadelphia: WB Saunders, 1983: 189–220.
6. Rosenblatt R, Pepitone-Rockwell F, Malcolm J, McKillop J. Continuous axillary analgesia for traumatic hand injury. Anesthesiology 1979;51: 565–6.
7. Manriquez RG, Pallares V. Continuous brachial plexus block for prolonged sympathectomy and control of pain. Anesth Analg 1978;57: 128–30.
8. Fortuna A, Fortuna AO. Narcoanalgesia: 1000 casos de anestesias combinadas (narcose + peridural ou raquianestesia). Rev Bras Anestesiol 1988;78:91–6.

More on Back Pain After Nesacaine-MPF

Key Words: ANESTHETICS, LOCAL—2-chloroprocaine. ANESTHETIC TECHNIQUES, EPIDURAL—2-chloroprocaine.

To the Editor:

We recently encountered a patient who developed painful muscular spasms after epidurally administered 2-chloroprocaine, an event that may serve to shed additional light on this interesting phenomenon as reported by Fibuch and Opper (1) and subsequent letters to the editor (2–4).

A 21-yr-old gravida two, para one white woman at term needed placement of an epidural catheter for management of pain during labor. Her pregnancy had been complicated only by severe nausea and vomiting during the first trimester. She had no significant medical history, took no prescription medications, and had had a prior epidural for labor without complication.

After subcutaneous infiltration with plain 1% lidocaine, an epidural catheter was easily placed at the fourth lumbar interspace and threaded 3 cm into the epidural space. The patient received a total of 8 mL of 0.25% bupivicaine (Sensorcaine) and 50 mg of fentanyl through the epidural catheter before an uncomplicated vaginal delivery. After delivery, the epidural catheter was left taped securely in position for use the following day when she was to return for an elective bilateral tubal ligation.

The next day the patient was brought to the operating room at 1 PM with her catheter taped securely in place. After a negative aspiration, a test dose of 5 mL of 2% 2-chloroprocaine (Nesacaine-MPF, Astra) was administered without evidence of subarachnoid or intravascular injection. Additional incremental doses up to a total of 35 mL of 2% 2-chloroprocaine was given to achieve a sensory level of anesthesia at the fifth thoracic dermatome. The tubal ligation was performed without complication and without the administration of any additional medications. At the conclusion of the procedure, the epidural catheter was removed intact.

At 2:10 PM the patient arrived in the recovery room with stable vital signs. Full return of motor function was documented at 2:45. At 3 PM, the patient first began to complain of pain upon motion of her legs. By 3:15, the pain had progressed to a constant cramping of the lower back bilaterally, with extension to both upper thighs. She was unable to assume any position that afforded relief and her obstetrician ordered that two Percocet tablets be given. At 3:40, one of us (T.M.M.) was called to see the patient, who was by this time in excruciating pain. Thorough sensory and motor examinations to rule out residual epidural blockade or epidural hematoma gave normal results. Because the patient's intravenous catheter had been removed by this time, 25 mg of meperidine was given intramuscularly and 5 mg of diazepam was given orally for analgesia and anxiolysis. A heating pad was also provided. By 4:15 PM the patient was able to lie still in bed, but she continued to complain of discomfort until about 8 PM, after which she was able to sleep through the night without recurrence.

Our case is an interesting addition to the report of Fibuch and Opper (in nonobstetrical patients) for several reasons. First, as acknowledged in their discussion, it was unclear whether the muscular spasms they noted were due to subcutaneous or intramuscular injection of local anesthetic solutions during infiltration, insertion of the epidural needle, and placement of the catheter. This could not have been the case in our patient because during placement of the epidural the day before, for relief of pain during vaginal delivery, a different local anesthetic solution (1% lidocaine) was used for identification of the epidural space. It is conceivable, although unlikely, that the 2-chloroprocaine local anesthetic solution may have leaked from the catheter as it was being removed a day later, after the tubal ligation had been performed. Perhaps more plausible would be the possibility that leakage from the epidural space into the paralumbar muscles occurred after catheter removal via a tract that may have formed while the catheter was in place. In any case, the time-course of the patient's complaints make it unlikely that her symptoms were due to effects of the 2-chloroprocaine itself; instead, the role of an additive such as the disodium ethylenediaminetetraacetic acid postulated by Fibuch and Opper appears more logical (1).

Fibuch and Opper failed to find back pain associated with epidural use of 2-chloroprocaine in obstetrical patients, suggesting that the more aggressive use of analgesics perioperatively in this group may have masked the effect. Schwalbe and Schiffmiller suggested this difference may also relate to physiologic differences between the pregnant and nonpregnant state (3). Our case documents this outcome in an obstetrical patient, and the persistence of her discomfort despite early narcotic therapy suggests that 2-chloroprocaine-induced muscular spasm can occur and persist in the presence of such therapy.

In summary, we confirm the observations of Fibuch and Opper and extend the description of muscular spasm after epidurally administered 2-chloroprocaine (Nesacaine-MPF) to an obstetrical patient who did not inadvertently receive intramuscular or subcutaneous local anesthetic solution.

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References

1. Fibuch EE, Opper SE. Back pain following epidurally administered Nesacaine-MPF. Anesth Analg 1989;69:113–5.
2. Ackerman WE III. Back pain after epidural Nesacaine-MPF (letter). Anesth Analg 1990;70:224–5.
3. Schwalbe SS, Schiffmiller MW. Back pain after epidural Nesacaine-MPF. Anesth Analg 1990;70:225.
4. Fibuch EE, Opper SE. Back pain after epidural Nesacaine-MPF. Anesth Analg 1990:70:225–6.

Missed Diagnosis of Cuff Herniation in a Modern Nasal Endotracheal Tube

Key Words: EQUIPMENT, CUFFS—endotracheal.

To the Editor:

There is an expectation that modern low-pressure high-volume endotracheal cuffs will not herniate and occlude inspiratory gas flow. This letter describes a 47-yr-old woman with extensive facial lacerations in whom this event was missed. She was scheduled for emergency plastic surgery. After a rapid sequence induction, a preformed 6.5-mm internal diameter Mallinckrodt nasal endotracheal tube (ETT) was passed with ease. The cuff was inflated with 6 mL room air. Its correct position was confirmed by auscultation. A throat pack was used to prevent soiling of the airway, and the tube was secured with adhesive tape. The patient was paralyzed and mechanically ventilated during the procedure. Monitoring included electrocardiogram, blood pressure, end-tidal carbon dioxide ($ETco_2$), and oxygen saturation (Sao_2).

During surgery, peak airway pressure increased from 20 to 60 cm of water and $ETco_2$ from 4.5 kPa (34 torr) to 6.5 kPa (49 torr); Sao_2 remained at 99%. Surgery was stopped. Manual ventilation was initiated. It became increasingly difficult, and widespread wheezes were heard throughout both lung fields. The throat pack was removed and the ETT inspected. It was not kinked and was correctly positioned. A drug reaction was considered because the patient had just received an injection of atracurium. Intravenous aminophylline did not reduce the airway pressure. During manual ventilation, a loud "pop" was heard, after which ventilation became easy. We changed the ETT and found a large hole in the cuff of the original tube (Figure 1). After this, surgery continued to a satisfactory conclusion.

It seems clear that the cause of our problem was mechanical in nature; a herniated cuff that partly occluded the distal end of the ETT was the probable cause. This obstruction cleared when the cuff burst. Our initial impression that there was bronchospasm was probably due to the turbulent airflow transmitted from the trachea. It is well recognized that nitrous oxide enters the cuffs of ETTs, increasing their size and on occasion causing them to herniate, which presumably occurred in this case. We failed to suspect cuff herniation because the cuff on a Mallinckrodt ETT is a low-pressure high-volume type and its distal border is positioned between 1.5 and 2 cm from the end of the ETT, the variation resulting from the beveled nature of the end of the tube. We were unable to produce cuff herniation in vitro with this type of tube using a 20-mL syringe to simulate the trachea. The cuffs on three tubes tested burst at volumes of 35, 38, and 39 mL room air. We failed to demonstrate cuff herniation in any of the tubes tested.

It is difficult to explain how the cuff herniation occurred in our original tube, and also to envisage how the initial 6

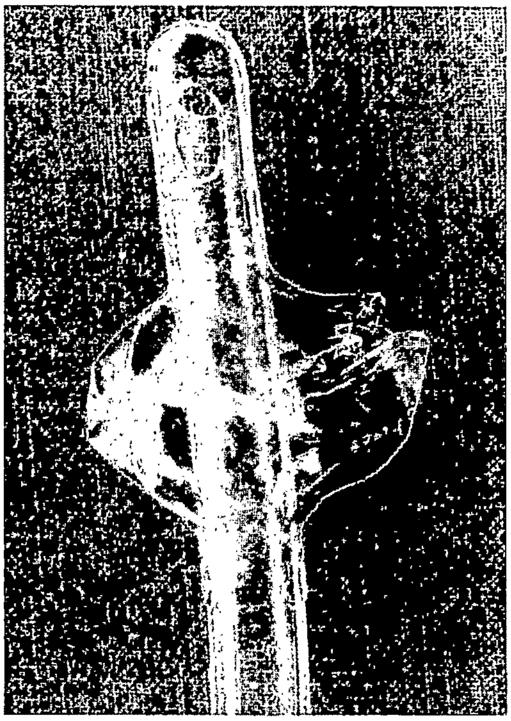

Figure 1. Nasal ETT with ruptured cuff shown. Note the distance of the cuff from the end of the tube.

mL of air in the cuff could expand to between 35 and 40 mL in 1 h. There may have been a fault in the cuff wall, one part of which was thinner than the rest, possibly causing disproportionate swelling in one area of the cuff by partly occluding the distal end of the ETT and allowing cuff rupture to occur at a low pressure.

We report this case to remind our colleagues that cuff herniation is still encountered even with modern-day ETTs.

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Does Sufentanil Produce Less Ventilatory Depression Than Fentanyl?

Key Words: ANALGESICS, SUFENTANIL, FENTANYL.

To the Editor:

A recent report by Bailey et al. implies that sufentanil may have a better margin of safety than does fentanyl—that is, it may achieve better analgesia with less ventilatory depression (1). Conventional wisdom holds that equipotent doses of the commonly used opioid analgesics produce equivalent degrees of ventilatory depression. Thus this report is of considerable interest.

The inference that sufentanil produces relatively less depression of breathing than does fentanyl is based solely on observed effects on the ventilatory response to added carbon dioxide (CO_2). However, the report suggests some important problems in the performance and/or analysis of this ventilatory test. First of all, the control values of the CO_2 response slope were statistically significantly different in the two study sessions used to assess separately the effects of each agent. Second, the assessment of the effects on the CO_2 response slope was based only on absolute changes from what appear to have been significantly variable control values. Third, the analysis as presented indicates that sufentanil and fentanyl had substantially different effects on the CO_2 response slope in relation to their effects on the resting end-tidal CO_2—that is, sufentanil appeared to cause less depression of the CO_2 response slope than did fentanyl (Figure 1 of the Bailey report) while producing a similar if not greater increase in end-tidal CO_2 (Figure 3 of the Bailey report). These indications of some problem in performing and/or analyzing the CO_2 response test, together with the previously stated hazards of interpreting CO_2 response data in isolation (2), lead one to question the reliability of these findings and the validity of the conclusion based on them.

Do the published results of this study permit any reasonable inference about the relative ventilatory depressant effects of equianalgesic doses of sufentanil and fentanyl? Administration of each opioid was followed by time-related changes in resting end-tidal CO_2 and the pain threshold. Because the control values of these variables appear not to have differed between study sessions, and because end-tidal CO_2 may be preferable to the CO_2 response as an index of ventilatory depression in any case (2), I have used the reported data on end-tidal CO_2 and pain threshold to examine the degree of ventilatory depression in relation to the varying levels of analgesia seen with each agent. Plots of the increments of end-tidal CO_2 versus the changes in pain threshold (Figure 1) suggest that at similar pain thresholds, sufentanil and fentanyl caused roughly equivalent increases in the end-tidal CO_2—especially at the higher pain thresholds (where the signal-to-noise ratio in the data was probably better). Unfortunately, the data used to construct these plots represent the averaged CO_2 and pain threshold differences produced by three different doses of each agent (the only data presented in the original report), and the analgesic potency of one or more of these three dose levels appears to have differed between agents (Figure 4 of the Bailey report). Accordingly, one cannot be confident about a conclusion based on these plots.

Thus, the data available from this study—as previously interpreted or as reinterpreted here—leave considerable uncertainty about the published conclusion that "sufentanil may provide better patient comfort with less respiratory depression than does fentanyl" (1). Perhaps the authors could provide additional information to help resolve this important issue—in particular, the separate values of

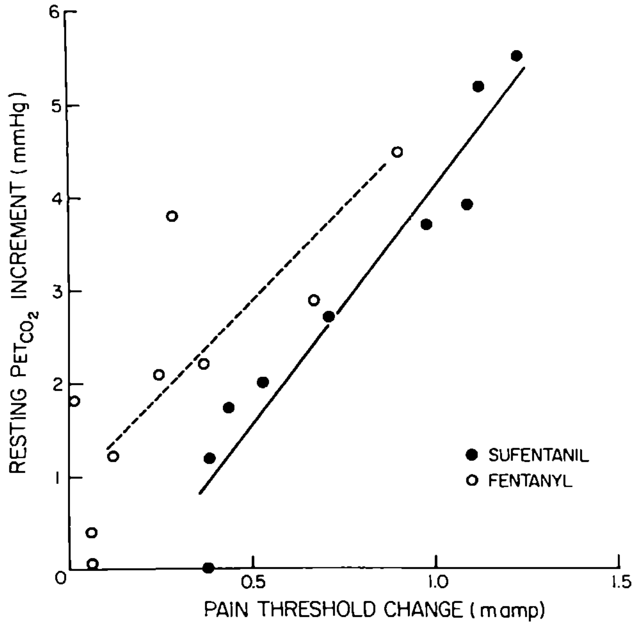

Figure 1. Ventilatory depression in relation to analgesia observed after sufentanil and fentanyl (data from Bailey et al. [1]). The ventilatory depressant effect is represented by increments in the end-tidal CO_2 (mm Hg) and the analgesic effect by changes in the pain threshold (milliamperes of electrical current that induced pain). The *points* indicate the averaged effects of three different doses of each agent. The *lines* depict the least-square linear regressions of each set of data points. (The *r* values for sufentanil and fentanyl data were 0.96 and 0.81, respectively).

$PETCO_2$ and pain threshold that were observed with each individual dose of sufentanil and fentanyl given. (It would be helpful to present the actual values of each variable observed rather than just the differences in values between the control and drug conditions.)

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References

1. Bailey PL, Streisand JB, East KA, et al. Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 1990;70:8–15.
2. Knill RL. Wresting or resting ventilation (letter). Anesthesiology 1983;59: 599–600.

In Response:

Dr. Knill has asked several questions that I had anticipated anesthesiologists with a healthy degree of skepticism would ask. I shall do my best to respond satisfactorily.

The qualified conclusion that "sufentanil *may* provide better patient comfort with less respiratory depression than fentanyl" was not based solely on observations of the ventilatory response to added CO_2 as Dr. Knill suggests. Occlusion pressure data agreed with ventilatory response data, and thus two different measures of respiratory drive produced results pointing to greater respiratory depression with the doses of fentanyl used than with the doses of sufentanil used.

Dr. Knill also points out that our report suggested some important problems in the performance and/or analysis of CO_2 challenges as a test of ventilatory drive. These "problems," or, as stated in our report, "causes of variability," were cited as factors that may have limited our ability to detect other significant differences, e.g., between drug dosage groups, but were not meant to imply that our data or its accumulation was flawed. Other authors, as indicated in the original manuscript, have also found a wide spectrum of normal responses to CO_2 challenges.

Drug dosage and order of administration assignments were both randomized and balanced in our study. Nevertheless, as Dr. Knill points out, the slopes of the ventilatory and occlusion pressure responses to CO_2 at baseline were different between the fentanyl and sufentanil groups. Although this was less than ideal, several appropriate statistical approaches exist for handling such data. One of those approaches is to analyze the change in the actual value minus the control value over time as we did (1).

A third criticism is that our CO_2 response data differ substantially from our resting end-tidal CO_2 data. I believe Dr. Knill implies that these differences indicate a problem with our performance and/or analysis of CO_2 response testing. However, there is no biological law that drug-induced changes in the resting end-tidal CO_2 must parallel changes in the slope of the CO_2 response tests or vice versa. In addition, the fact that we could find no difference in resting end-tidal CO_2 between the sufentanil and fentanyl groups would also point to an advantage with sufentanil, as it provided greater analgesia. I believe it is important to distinguish and define the importance of resting end-tidal CO_2 as well as both ventilatory and occlusion pressure responses to CO_2 challenges. The relative importance of these variables has been debated in the past (2,3). An elevated resting end-tidal CO_2 or arterial CO_2 can surely be caused by drug-induced ventilatory depression. The ventilatory and occlusion pressure responses to CO_2 challenges, although rarely measured in the everyday clinical setting, are perhaps more sensitive measures of ventilatory control (2). In addition, these responses tell us how the brainstem will respond to serious increases in arterial CO_2 tensions. Doses of drugs that result in extremely low slopes of the ventilatory and occlusion pressure responses to CO_2 indicate a degree of depression that will most likely lead to CO_2 accumulation, CO_2 narcosis, and further ventilatory depression. Thus, although the resting end-tidal CO_2 is the more tangible and clinically used variable, CO_2 response data also provide valuable information.

Dr. Knill requests additional data and believes plots of the resting end-tidal CO_2 versus the pain threshold for each drug dosage group will be revealing. A plot of the resting end-tidal CO_2 versus pain threshold for fentanyl (2 μg/kg)

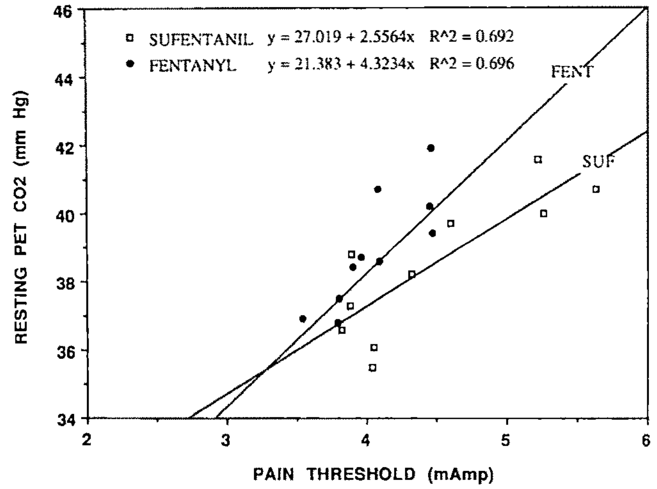

Figure 1. Graphic plot of the resting end-tidal CO_2 (mm Hg) versus pain threshold (mA) for sufentanil (0.2 μg/kg) and fentanyl (2 μg/kg). The slope for sufentanil is less than that for fentanyl and indicates that pain threshold (analgesia) rises faster than the resting end-tidal CO_2 with sufentanil than it does with fentanyl.

and sufentanil (0.2 μg/kg) is illustrated in Figure 1. The greater slope for fentanyl (4.3) compared to sufentanil (2.6) indicates that more respiratory depression for a given degree of analgesia occurred after fentanyl than after sufentanil. A plot of the 1 μg/kg fentanyl versus 0.1 μg/kg sufentanil produced similar results (fentanyl slope, 3.4; sufentanil slope, 2.8), whereas the highest doses produced the opposite result (fentanyl slope, 2.0; sufentanil slope, 3.9). Thus, although no statistical significance was reached with these particular results, they are, overall, consistent with our conclusion. These data have been forwarded to Dr. Knill as he requested.

I commend Dr. Knill for his healthy degree of skepticism. I invite him to evaluate the hypothesis that sufentanil may provide better patient comfort with less respiratory depression than fentanyl in the setting of his choice. Although this hypothesis is not consistent with current conventional wisdom, in the future it will hopefully be the conventional wisdom, if not for opioids, then for other potent analgesic agents.

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References

1. Kaiser L. Adjusting for baseline: change or percentage change. Stat Med 1989;8:1183–90.
2. Gross JB. Resting ventilation measurements may be misleading (letter). Anesthesiology 1984;61:110.
3. Knill RL. Wresting or resting ventilation (letter). Anesthesiology 1983;59: 599–600.

Preventing Unauthorized Access to Narcotics in the Operating Room

Key Words: ANALGESICS, CONTROL OF ACCESS TO NARCOTICS.

To the Editor:

Narcotic abuse and diversion remain the number-one health risk for practicing anesthesiologists. One factor in reducing and detecting narcotic diversion is accurate narcotic accountability. Most narcotic sign-out and drug accountability systems do not address the loss of narcotics after they are signed out. "Loss" of narcotics either through carelessness or through theft can label an anesthesiologist as suspect.

For instance, in our hospital, until recently, narcotics were signed out from the pharmacy as a standardized pack each morning and anesthesiologists returned the excess and wastage at the end of the day along with a worksheet documenting usage. Two apparent thefts of such packs occurred recently, within a week. In both instances, the narcotics were left unattended for a few minutes in the operating room while the anesthesiologists transported patients to the recovery room. Under the circumstances, it was impossible to identify the source of the diversion.

As a response to this problem, we instituted the following simple solution for both the operating room and the obstetrical anesthesia services. Narcotic packs are signed out each morning from the pharmacy in individual soft "fanny packs" that can be worn around the waist and have become popular worldwide as a hands-free purse (Figure 1). Anesthesiologists wear their narcotic pack throughout the day, so that narcotics are never left unattended. The packs are returned to the pharmacy at the end of the day and restocked. Packs can be equipped with tamper-proof seals to indicate whether they have been opened. Color coding of the packs for regular cases and for high-dose narcotic cases allows easy stocking. Accounting and reporting of wastage are as before. We find this system far more convenient and comfortable than individual lockboxes (which are invariably left unattended when the anesthesiologist leaves the room) or case-by-case sign-out of narcot-

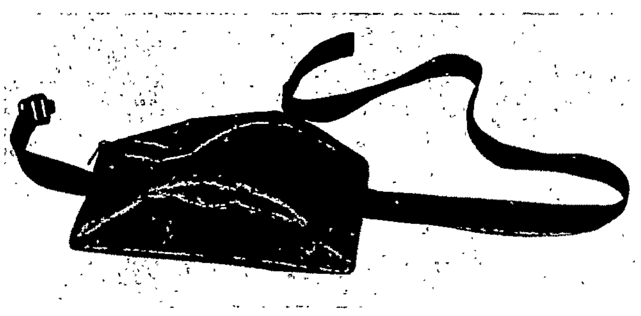

Figure 1. "Fanny Pack" worn by anesthesia personnel to make narcotics available and to limit access to authorized individuals only.

ics (which requires full-time pharmacy support in the operating room). Another advantage of the system is that anesthesiologists may take a supply of narcotics with them when delivering anesthesia in ancillary care locations such as the cardiac catheterization laboratory or radiology.

Physician and nurse acceptance of the system has been excellent, and return of the "fanny packs" each night assures their availability for restocking.

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Mixed Venous Oximetry May Detect Critical Oxygen Delivery

Key Words: BLOOD, HEMODILUTION—isovolemic.

To the Editor:

Trouwborst and coworkers, in their study of changes in mixed venous blood oxygenation during normoxic acute isovolemic hemodilution (1), found that with progressive hemodilution oxygen uptake remained unchanged despite gradual decrease in oxygen delivery, until a point of critical oxygen delivery was reached. Thereafter, further hemodilution decreased both oxygen delivery and oxygen uptake. Above and below the critical oxygen delivery, the relationship between oxygen delivery and oxygen uptake seemed to be linear, the slope of the line being essentially zero above the critical oxygen delivery and positive below it. The average mixed venous oxyhemoglobin saturation ($S\bar{v}O_2$) corresponding to the critical oxygen delivery was 44% ± 8%. In the opinion of Trouwborst et al., monitoring $S\bar{v}O_2$ would be helpful in the assessment of changes in tissue oxygenation during hemodilution.

After fiberoptic pulmonary artery catheters became available, acceptance of $S\bar{v}O_2$ monitoring into critical care medicine was sluggish, largely as a result of failed attempts to use the $S\bar{v}O_2$ monitor to estimate cardiac output. However, the use of fiberoptic pulmonary artery catheters spread widely after Nelson demonstrated the close association between $S\bar{v}O_2$ and the oxygen extraction ratio (O_2ER) (2). By estimating oxygen extraction, the ratio of oxygen uptake ($\dot{V}O_2$) and oxygen delivery ($\dot{D}O_2$), one could determine whether the patient's hemoglobin concentration, arterial blood oxyhemoglobin saturation, and systemic blood flow were adequate with respect to tissue oxygen uptake. This analysis was based on the assumption that in most, if not all, clinical situations, oxygen uptake does not depend on oxygen delivery. Recently, several experimental and clinical studies have demonstrated that delivery dependency of oxygen uptake may appear when oxygen delivery is lowered even within a clinically relevant range. In fact, in some clinical situations, delivery dependency exists at all levels of oxygen delivery. These findings have discouraged clinicians from using fiberoptic pulmonary artery catheters and $S\bar{v}O_2$ monitoring.

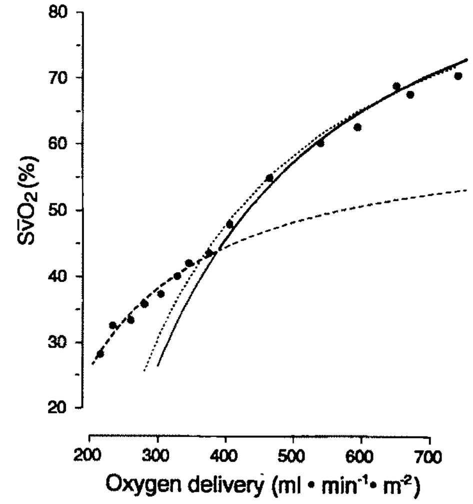

Figure 1. Observed changes in mixed venous oxyhemoglobin saturation (*dots*) plotted as a function of oxygen delivery during hemodilution in pigs (data from Trouwborst et al., Reference 1). The *continuous line* represents the expected change in $S\bar{v}O_2$ calculated from oxygen uptake and delivery above critical oxygen delivery. The *dashed line* delineates the expected response when oxygen uptake is delivery-dependent. The *dotted line* represents the expected response calculated from one set of baseline oxygen uptake and delivery values, assuming that oxygen delivery remains unchanged. The observed $S\bar{v}O_2$ values begin to deviate from the response expected for delivery-independent oxygen uptake at the point of critical oxygen delivery.

The data Trouwborst et al. present seem to indicate that the relevance of $S\bar{v}O_2$ is not lost even when oxygen uptake becomes delivery-dependent. In their study, $S\bar{v}O_2$ continued to decrease in an almost linear fashion even when oxygen delivery was lowered below the critical point (Figure 1). Therefore, monitoring of $S\bar{v}O_2$ continued to reflect worsening tissue oxygen supply-demand conditions even when uptake was delivery-dependent.

A closer analysis of the relationship between $S\bar{v}O_2$ and oxygen delivery reveals that this relationship is best described by two hyperbolic curves that intersect at the point of critical oxygen delivery. Because the relationship between oxygen uptake and delivery is very close to linear, it can be described using the formula

$$\dot{V}O_2 = a\cdot\dot{D}O_2 + b,$$

where a and b are constants. Because $O_2ER = \dot{V}O_2/\dot{D}O_2$, oxygen extraction can be expressed as a function of oxygen delivery by combining the two formulas:

$$O_2ER = \frac{b}{\dot{D}O_2} + a.$$

Assuming full oxygen saturation of arterial blood hemoglobin (3),

$$O_2ER \approx 1 - S\bar{v}O_2$$

and

$$S\bar{v}O_2 \approx 1 - a - \frac{b}{\dot{D}O_2}.$$

This formula defines a hyperbolic curve, regardless of whether oxygen uptake is delivery-dependent ($a > 0$) or delivery-independent ($a = 0$). Because constants a and b have different values on different sides of the point of critical oxygen delivery, two separate hyperbolic curves apply to the range of oxygen delivery in the study of Trouwborst et al. (Figure 1). The average $S\bar{v}O_2$ values reported in their paper follow very precisely the two hyperbolic curves generated from the corresponding average oxygen delivery and oxygen uptake data.

Theoretically, one could predict the changes in $S\bar{v}O_2$ secondary to decreased oxygen delivery, given initial values of oxygen delivery and uptake and assuming that oxygen uptake remains unchanged thereafter. Such a prediction is also supported by the data of Trouwborst et al. At the point of critical oxygen delivery, $S\bar{v}O_2$ values would deviate from this prediction and begin to follow a new relationship defined by delivery-dependent oxygen uptake. This deviation should occur at the point of critical oxygen delivery, allowing accurate detection of this point in individual subjects.

This technique might provide a better limit of hemodilution than an average critical $S\bar{v}O_2$ calculated from a population with considerable intersubject variability. However, a clinical study is required to validate this approach before it can be used as a basis for interpreting observed changes in $S\bar{v}O_2$.

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References

1. Trouwborst A, Tenbrinck R, Van Woerkens EZ. Blood gas analysis of mixed venous blood during normoxic acute isovolemic hemodilution in pigs. Anesth Analg 1990;70:523–9.
2. Nelson LD. Continuous venous oximetry in surgical patients. Ann Surg 1986;203:329–3.
3. Räsänen J, Downs JB, Dehaven B, Seidman P. Estimation of oxygen utilization by dual oximetry. Ann Surg 1987;206:621–3.

Extremity Tourniquet Deflation Increases End-Tidal P_{CO_2}

Key Words: EQUIPMENT, TOURNIQUET—effects of deflation.

To the Editor:

I congratulate Dickson et al. for their study of the acute increase in end-tidal partial pressure of carbon dioxide (ET P_{CO_2}) after the release of an extremity tourniquet during orthopedic surgery (1). To establish an accurate bibliography on the effect of tourniquet deflation on ET P_{CO_2}, I would like to point out that two publications on the subject, one by Patel et al. (2), another by Deen and associates (3), preceded that by Dickson et al.

The time after tourniquet deflation at which patients were studied differed in the three papers. Dickson et al. terminated their study at 5 min, Deen et al. at 30 min, and Patel et al. when ET CO_2 returned to baseline predeflation values, which averaged 13 min 7 s ± 5 min 17 s. The latter two studies found that arterial CO_2 tensions increased concomitantly with the increase in ET CO_2 and Patel et al. reported that Pa_{CO_2} was still elevated when ET CO_2 had returned to baseline. Patel et al. also reported decreases in pH greater than the expected 0.05 U for each 10 mm Hg increase in Pa_{CO_2}, indicating a metabolic component in the alteration of pH.

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References

1. Dickson M, White H, Kinney W, Kambam JR. Extremity tourniquet deflation increases end-tidal P_{CO_2}. Anesth Analg 1990;70:457–8.
2. Patel AJ, Choi CS, Giuffrida JG. Changes in end tidal CO_2 and arterial blood gas levels after release of tourniquet. South Med J 1987;80:213–6.
3. Deen L, Nyst CLTM, Zurrmond WWA. Metabolic changes after tourniquet release. Acta Anaesthesiol Belg 1982;33:107–14.

Doppler Detection of Intravenous Mannitol Crystals Mimics Venous Air Embolism

Key Words: EMBOLISM, AIR—mimicked by mannitol crystals. KIDNEY, DIURETICS—mannitol and air embolism.

To the Editor:

By far the most common cause of changes in the precordial Doppler tones during craniotomy is venous air embolism (VAE). Another cause is injection of medications and associated microbubbles through a central catheter. In the following unusual case the cause of the Doppler changes was infusion of 20% mannitol in which tiny crystals had formed.

The patient was a 73-yr-old man undergoing a right frontal craniotomy for tumor resection. The surgical position was supine with a head-up tilt of 15°–20°. After completion of the skin incision and during elevation of the skin flap, a loud and continuous shift was heard on the Doppler consistent with VAE. The patient was placed in the slightly head-down position by the surgical team as they sought to identify the source of air entrainment in the wound. Doppler changes consistent with VAE were still heard after the patient was placed head-down. During

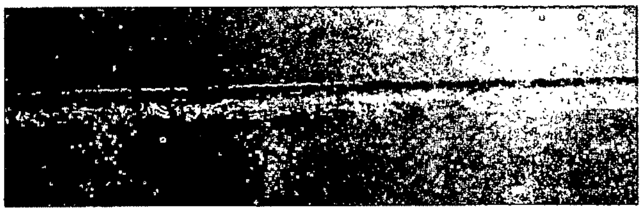

Figure 1

evaluation of this problem the mannitol and intravenous tubing through which it was being infused were found to contain crystals (Figure 1). The mannitol infusion was discontinued and the Doppler changes cleared. There were no changes in end-tidal carbon dioxide or blood pressure associated with the Doppler changes. Reinstitution of the mannitol infusion produced Doppler changes similar to those heard previously. The mannitol and its intravenous tubing were discarded and replaced with an infusion free of crystals. The patient was returned to the head-up tilt position and no further Doppler changes were noted throughout the case. The patient suffered no apparent sequelae.

Crystallization can occur in mannitol solutions of 20% or greater at room temperature. Mannitol solutions should be carefully inspected before being infused.

Changes in precordial Doppler sounds may be due to causes other than VAE. Changes can be produced by any venous embolism, including mannitol crystals, that reflects the ultrasound waves emitted by the Doppler device.

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A Simple Method for Reducing Backup of Blood Into Intravenous Lines Caused by Inflation of a Blood Pressure Cuff

Key Words: EQUIPMENT, BLOOD PRESSURE CUFF —intravenous lines.

To the Editor:

There are numerous times when an anesthesiologist may find it necessary or convenient to place an intravenous (IV) catheter and a blood pressure cuff on the same extremity. This usually results, however, in interruption of IV fluid flow and retrograde flow of blood into the IV line upon inflation of the blood pressure cuff. We describe a method for preventing backup that, to the best of our knowledge, has not been previously described in the literature.

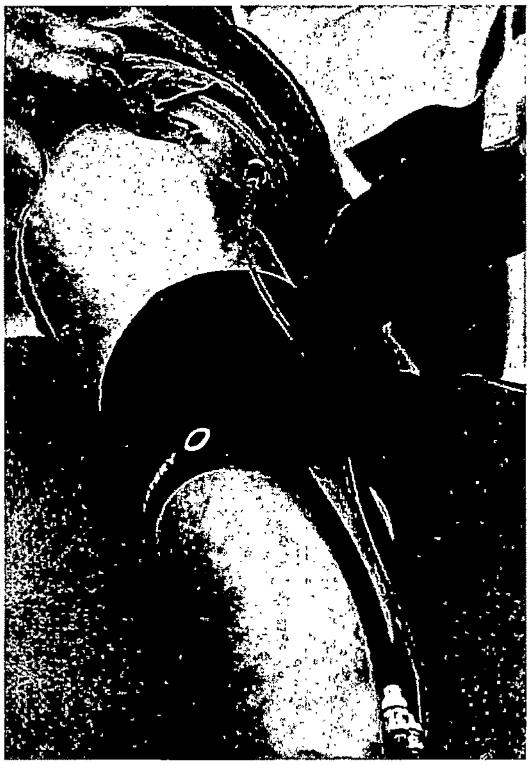

Figure 1. Position of IV tubing in blood pressure cuff to reduce backup of blood into the intravenous tubing.

After starting the IV infusion and putting the blood pressure cuff in place, partially open the Velcro closure on the cuff and place a length of the IV fluid line tubing across the cuff as close as practical to the cuff's air bladder (Figure 1). Close the Velcro over the tubing. Subsequent inflation of the cuff exerts pressure on the enclosed segment of tubing, which prevents venous blood from flowing retrogradely into the IV tubing.

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Book Reviews

Pediatric Anesthesia, 2nd ed.

G. A. Gregory, ed. New York: Churchill Livingstone, 1989, 1388 pp, $125.00.

The first edition of *Pediatric Anesthesia* (1983) was notable for its publication at a time when the subspecialty was in need of a comprehensive and authoritative textbook. The second edition is similar to the first in its goals and structure, and consists of two complimentary volumes, the first on fundamental topics and the second on specific clinical problems. Most of the original 30 chapters have been updated, and six new chapters have been added. Any pediatric anesthesiologist will be impressed by the list of chapters and 37 contributors, and will not be disappointed by about four-fifths of the chapters. Unfortunately, one-fifth of the chapters is so incomplete, outdated, inaccurate, or misleading that the book's potential as the authoritative overview of pediatric anesthesia is not achieved.

If selective, the reader will be well rewarded by chapters that are superbly written, thorough, and authoritative. The chapters on the respiratory system and the renal system make embryology and physiology intriguing. "Developmental Metabolism and Nutrition" is filled with historical developments, controversies, and common clinical implications likely to appeal to even the most biochemistry-phobic among us. The essentials of safe practice are concentrated in the chapters on malignant hyperthermia, equipment, psychological preparation and premedication, maintenance of anesthesia, recovery room, regional anesthesia, outpatient anesthesia, and a progressive chapter on pain management. Chapters on special techniques, congenital heart, thoracic, neuro, genitourinary, eye, ENT, plastic, and orthopedic surgery are packed with useful facts and sophisticated discussions of issues and priorities. An exceptional chapter on intensive care is concise yet 82 pages long, covering a wide variety of subjects including the only discussion of cardiopulmonary resuscitation in this book and valuable sections on monitoring, vascular access, shock, and inotropes.

On the other hand, many common clinical problems are given insufficient attention or entirely neglected. Altogether, less than one page is devoted to the evaluation, potential complications, and disposition of children with acute or subacute upper respiratory infections. Explicit recommendations for the duration of preoperative fasting for various age groups or for preoperative screening tests in healthy children are lacking. Although routine urinalysis is discouraged as a screening test in the chapter on the renal system, the chapter on preoperative evaluation states that "a routine urinalysis, including specific gravity, should be available on all patients." This chapter provides just one sentence on unsuspected murmurs and nothing on asthma. Surprisingly, no chapter discusses anesthesia for CT scan, myelogram, cardiac catheterization, balloon angioplasty, pericardial tamponade, heart transplantation, cardiomyopathy, pacemaker insertion, hypoplastic left heart syndrome, liver transplantation, organ donation, or intussusception.

Seven chapters suggest that the $\mathrm{Pao_2}$ be maintained in the normal range (some say 50–70, others say 60–90 mm Hg) to reduce the likelihood of RLF during anesthesia for neonates below 44 wk postconceptual age. This advice is not qualified by any margin of safety during transport or surgery, when the $\mathrm{Pao_2}$ is likely to decrease because of hypoventilation, lung retraction, endotracheal tube displacement, or low cardiac output. The chapter on genitourinary surgery is the only one to place the theoretical concern about a short-term exposure to hyperoxia in perspective, and only one of two chapters that refer to retinopathy of prematurity, the current terminology.

Many basic chapters have not been updated, especially regarding pulse oximetry and end-tidal $\mathrm{CO_2}$ monitoring. Within the chapter on monitoring, the discussion of tetralogy of Fallot monitoring ends with a statement that "despite the fact that this machine is sometimes difficult to calibrate and somewhat finicky, it is worth the trouble," followed by a discussion of pulse oximetry that does not reveal a preference for it or even encourage its use for all patients. Although end-tidal $\mathrm{CO_2}$ monitoring is discussed, there is no mention of its value in detecting disconnection, esophageal intubation, or rebreathing. Additionally, there is no statement that it is mandatory or encouraged for all intubated patients. Similarly, the chapter on design of the operating room does not mention oximetry as a standard monitor in the operating room or recovery room, the chapter on the recovery room does not mandate its use for every patient, and neither the chapter on the recovery room nor the one on outpatient anesthesia refers to oxygen saturation as one of the criteria for discharge from the recovery room.

Examples of some of the inaccurate or misleading statements are: "infants are considered premature if they are

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born before 38 weeks gestational age or weigh less than 2500 gms at birth"; 0.2 mg/kg propranolol for TET spells; 100–200 mg/kg calcium gluconate over 2–3 min for hypocalcemia; "cuffed tubes may be used, even for a neonate or infant"; "nitrous oxide *may* be contraindicated in neonates with necrotizing enterocolitis"; "donor blood must be tested for a VDRL and hepatitis B antigen" (without mentioning HIV, CMV, or surrogate testing); "only once has rectal methohexital been associated with apnea"; "at times the tachycardia (from pancuronium) is severe enough to cause congestive heart failure"; "the Cole tube is no longer in common use" (rather than no longer recommended); "red rubber tubes remain in use" (rather than condemning them or discouraging their use except for laser surgery); 20-gauge intraarterial catheters should be used for all patients ≥3 kg; and "the operating room should be warmed to 32–37°C for patients weighing less than 10 kg and to 25–28°C for larger patients."

The text contains very few typographical errors. All are obvious except on p. 221, where the word should be "semi-starvation," and on p. 408, where the word should be "thiopental." The paper and binding are excellent. Most illustrations are good although some photographs and x-rays did not reproduce well.

In conclusion, Gregory's textbook has many strong features. It will be extremely valuable to full-time pediatric anesthesiologists and others who are sophisticated enough to recognize its limitations. One detailed discussion on important issues such as URI, NPO, retinopathy of prematurity, monitoring standards, quality assurance, postoperative apnea, and intraoperative hazards would have been particularly helpful to those looking for an introduction to the specialty.

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Anesthesiology and the Heart

T. H. Stanley, R. J. Sperry, eds. Boston: Kluwer Academic Publisher, 1990, 346 pp, $115.00.

This book is the hardcover collection of manuscripts used in the Refresher Course presentations given at the Thirty-Fifth Annual Postgraduate Course in Anesthesiology, which was held in Snowbird, Utah, in February 1990. Why publish such a collection of lecture notes? The editors' stated purpose is that the book is to serve (a) as a reference for those who attended the meeting, and (b) as a vehicle for bringing the latest concepts in anesthesiology to others within a short time after the presentations. In this day of fax machines and laser printers, is such a vehicle necessary?

The 28 chapters are published in the same style as the ASA Annual Refresher Course Lectures. Most of the chapters are well-written and cover the important clinical aspects of their stated title. Little information has been rushed from the lab or operating room to this book. These presentations were given by well-known anesthesiologists speaking on the specific topics for which we know them well.

Several chapters are particularly well-written and concise, including the chapters on preoperative hypokalemia, evaluation of right ventricular function, calcium channel blocking drugs, and the physiology of congenital heart disease. Two separate chapters reviewing the literature concerning the use of isoflurane and coronary steal are worth reading. The chapter on anesthesia for vascular surgery, although well-written, is better covered by the same author in a recent textbook.

Several chapters are poorly written, superficial discussions that are poorly referenced. Several misspellings, a missing table, and scarcely titled tables were observed. One chapter consists of a reprint of a 1988 journal editorial.

In summary, this book includes an eclectic collection of Refresher Course presentations. The same information is available in a much more polished, complete form in several recently published anesthesia textbooks.

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Memory and Awareness in Anesthesia

Benno Bonke, William Fitch, and Keith Millar, eds. Berwyn, Pa.: Swets and Zeitlinger, 1990, 394 pp, $60.00.

This substantial volume represents the publication of the proceedings of the First International Symposium on Memory and Awareness in Anesthesia held in Glasgow, Scotland, April 6–8, 1989. The organizers of that meeting did an admirable job of bringing together experts with both research-oriented and clinical interest in the problem of awareness and recall. The papers are, as a group, notable for the creative breadth of the presentations. As one often sees with such a compendium, there is a certain amount of unevenness. However, the editors managed to organize the 50 papers in broad categories that lend coherence to the project.

What distinguishes this opus from others is its focus on the psychological experience of the patient and on the management of awareness and recall by the anesthesiologist when they do occur. There is an entire section devoted to just these issues.

Many of the papers in this compendium focus on the distinction between implicit and explicit memory. The idea is presented that, even if there is no verbal recollection of intraoperative events, nonverbal memory traces may still be present in the central nervous system. The pioneering work of Henry L. Bennett in this area lends credibility and currency to this idea. What is most exciting to this reviewer is that the premise that remembering may occur at a nonverbal level brings scientific anesthesiology closer to the ideas of the dynamic unconscious as propounded by Freud and others. It suggests that the gap between neurophysiologic materialism and psychology is gradually narrowing. With each passing year, the literature of psychiatry becomes more neurophysiologically oriented as the literature of anesthesiology begins to add psychological considerations to its purview. This may reflect the realization that it is in the interstices of mind/body dualism that the truth can be found.

The continuum of mental states between consciousness and unconsciousness that is evoked by anesthetics provides a fertile laboratory for the exploration of the mind/body problem. Measuring and describing aspects of changing consciousness under the controlled circumstances of the administration of anesthetic drugs will eventually yield much information about the relationship between the brain's biological and psychological states. The contribution that can be seen for the understanding of human behavior is limitless. This science is in its infancy; the implications for the future of humankind are enormous. The researchers who presented their work at this meeting are pioneers.

The value of this book for the generalist in anesthesia rests in the humanization of anesthesiology as a specialty. It points the way to a study of anesthesia and its processes that admits a broader view of the work of the anesthesiologist than has ever been available before. For those with a philosophical bent, this work presents a practical laboratory for the testing of theoretical viewpoints.

We can look forward with eager anticipation to future work in this important area. This is not one of those books that will add to the technical proficiency of the anesthesiologist. There are plenty of those around. This is one that will, however, deepen the anesthesiologist's insight into the nature of what he or she does. For that reason, this is a book that can be recommended to all anesthesiologists.

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Protection of the Brain From Ischemia. Current Neurological Practice Series

P. R. Weinstein and A. I. Faden, eds. Baltimore: Williams & Wilkins, 1990, 307 pp, $85.00.

The recent information explosion concerning the pathomechanisms, diagnosis, and treatment of brain ischemia has provided a challenge to those hoping to keep up with new developments and syntheses of ideas. Correspondingly, the task of organizing a book on this topic has been formidable, and until now a thorough multidisciplinary printed source of information has been unavailable. Weinstein and Faden have succeeded in incorporating the major components of the field of brain protection into one book, which has been edited with the concerns of perioperative stroke held in central focus. Although it is perhaps most specifically directed toward the neurosurgical audience, there is considerable overlap among disciplines, which makes this text of interest to many anesthesiologists.

The book is organized into four sections: Pathophysiology, Diagnosis, Clinical Problems, and Protective Therapies. Each section has contributions from numerous individuals with widely recognized expertise in the specific subheadings. For example, in the pathophysiology section, cerebral blood flow is discussed by N. A. Lassen and J. Astrup, and the hemodynamics of postischemic reperfusion is discussed by K-A. Hossman. The chapter on glycolytic metabolism in brain ischemia (i.e., the glucose question) by M. D. Ginsberg is perhaps the best-written on this subject to date. In the diagnosis section, a relatively elementary chapter is provided on CT/MRI imaging of ischemic/infarcted brain, but this section (with many clearly illustrative images) is also comprehensive and provides a valuable update.

In the clinical problems section, a chapter is included advising on management procedures for stroke and is useful because it refers primarily to modalities of treatment that are accepted and available. The chapter on brain trauma and ischemia concentrates on the perils of secondary injury after head trauma such as hypoxia. The author (L. H. Pitts) demonstrates how the effect of these combined insults is more than additive and that prevention of such is readily obtainable. In the protective therapies section, most of the chapters focus on the frontiers of pathomechanisms and pharmacology of brain ischemia, although some practical information is also presented. For example, the chapter on optimal anesthetic management of patients at risk for cerebral ischemia by McPherson et al. is successful in presenting, in an accurate and unbiased fashion, what is known about ischemia/anesthetic interactions. Another chapter on barbiturate therapy, unfortunately, is primarily anecdotal and offers little insight into what is unique about these cerebral metabolic rate depressants. The only other shortcoming of this book is the lack of discussion of moderate hypothermia to which considerable attention has been paid over the past several years as a potential low-risk modality for brain protection. The fact that a discussion of deep hypothermia, as may occur with cardiopulmonary bypass, is entirely absent does identify this book as focusing on disease, which is approachable by neurosurgical procedures. This book is excellent and is highly recommended to serve either as an introduction or as a review to readers interested in having current knowledge of perioperative brain ischemia.

David S. Warner, MD
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Iowa City, Iowa

Anesthesiology: Specialty Board Review, 3rd ed.

T. P. Beach. Norwalk, Conn.: Appleton & Lange, 1990, 305 pp, $39.95.

This reviewer was provided an opportunity to use this book as part of preparation for the written boards. Was the opportunity beneficial? The subspecialties were fairly well-covered, with satisfactory answers and good references.

Indeed, some of the questions on the written boards were quite similar to those in the book. One criticism of the format is that the "review" that preceded each of the 14 categories was too short to be of any subsequent value in preparing to answer the questions that followed.

Monique Mabey, MD
University of Pennsylvania
Philadelphia, Pennsylvania

Neuroanesthesia

S. S. Porter, ed. Philadelphia: J. B. Lippincott, 1990, 236 pp, $30.00 single issue, $65.00 annual subscription for four issues of Problems in Anesthesia series.

The major focus of this book is to provide those residents or practitioners who intermittently administer anesthesia for neurosurgical procedures with a concise and practical approach to common neuroanesthesia problems. Most chapters describe the pathophysiology, preoperative evaluation, essential anesthetic considerations, anesthetic techniques, and postoperative management of various neurosurgical diseases. As a result, the chapters effectively apply basic physiologic and pharmacologic principles to the clinical management of neurosurgical patients in a problem-oriented manner.

This multiauthored text contains 13 chapters that describe the basics of cerebral physiology and metabolism; electrophysiologic monitoring of the central nervous system; head and spinal cord injury; anesthesia for children and adults with increased intracranial pressure, cerebral aneurysm clipping, posterior fossa procedures, and cerebrovascular disease; pediatric neuroanesthesia; preoperative evaluation; postoperative neurosurgical intensive care; and neurodiagnostic imaging. Some chapters are particularly well-written and provide outstanding overviews of common clinical concerns, especially "Anesthesia for Cerebral Aneurysms and Arteriovenous Malformations" and "Anesthesia for Spinal Cord Injury." "Electrophysiologic Monitoring of the Central Nervous System," "Anesthesia for Increased Intracranial Pressure in Adults," and "Neurodiagnostic Imaging" are also very readable and informative for the general anesthesiologist.

My major criticism with the book is that there is a disturbing degree of overlap between chapters. The preoperative evaluation and postoperative neurosurgical intensive care chapters are virtually unnecessary because the other disease process chapters consider relevant preoperative and postoperative care within their context. The chapters on anesthesia for increased intracranial pressure in pediatrics and pediatric neuroanesthesia also cover similar material. Of lesser importance, anesthetic effects on cerebral physiology, treatment of increased intracranial pressure, and electrophysiology are discussed to varying degrees in multiple locations.

If the redundancy were to be eliminated, additional chapters, such as anesthesia for epilepsy surgery (including pro- and anticonvulsant effects of anesthetics), anesthesia for transsphenoidal hypophysectomy, and deliberate hypotension, could be added. This would result in a more comprehensive text without sacrificing the brevity and simplicity that are the main features of this book.

Despite the above criticism, *Neuroanesthesia* is a succinct, highly readable, clinically relevant, problem-oriented introductory neuroanesthesia text. It highlights areas of controversy and successfully integrates basic physiology with essential perioperative considerations in neurosurgical patients. The book is highly recommended to residents during their month-long neuroanesthesia rotation and to busy practitioners who desire an update in neurosurgical anesthesia.

Karen B. Domino, MD
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Seattle, Washington

Watchful Care: A History of America's Nurse Anesthetists

Marianne Bankert. New York: The Continuum Publishing Co., 1989, 234 pp, $24.95.

The subject of nurse anesthesia generates strong feelings among anesthesiologists, especially recently. When faced with such a controversial situation, historical analysis often both yields useful information about why and how the situation developed and leads to a new understanding. This book provides new information about the development of nurse anesthesia and thus gives us a new understanding of the controversy.

The last historical analysis of nurse anesthesia, Virginia S. Thatcher's *History of Anesthesia, With Emphasis on the Nurse Specialist*, was published in 1953. *Watchful Care* reviews the time period covered by Thatcher and continues to the present. Sources used are both secondary material, such as Thatcher's work and *The Genesis of Contemporary Anesthesiology* by Volpitto and Vandam, primary material (letters, speeches, and interviews) in the archives of the American Association of Nurse Anesthetists (AANA), and bulletins and journals published by the AANA.

The author, former chair of a college English department and active in the area of women's studies, was hired by the AANA to prepare a new history of nurse anesthesia. Her approach was to broaden Thatcher's previous historical examination to include the social and economic factors leading to nurse anesthesia and also to explore why nurse anesthetists were historically "invisible" until recently.

This approach is most successful in its treatment of the early years of nurse anesthesia. Bankert documents that nurses (all female at the time) entered anesthesia because most doctors (male) were not interested in anesthesia, primarily for economic reasons. The importance of hospital administrators—through both the American Hospital Association (which fostered development of the first nurse anesthesia organization) and through individual efforts (John Mannix, Assistant Director of University Hospitals in

Cleveland, provided critical support for the formation of the first organization)—is well-documented. This support from administrators had an economic basis also: hospital administrators were as interested in controlling costs in the 1920s as today, and nurse anesthesia was cheaper than physician anesthesia.

As the book proceeds, there is less strong documentation of the effect of social and economic factors, especially for recent events. Although important events are chronicled, the causative factors are not always clear. There are good sections on the early development of anesthesia and surgery and the development of American nursing. A summary of legal actions related to nurse anesthesia is the best and most easily accessible account to be found.

What problems resulted from the increasing number of male anesthetists after World War II? There *had* to be conflict as men took over leadership roles in the AANA. Men were first admitted to the AANA in 1947, and there have been five male AANA presidents since 1972. It would have been interesting to look at the percent of male members in the organization as these changes in leadership occurred and to document the conflict generated by this change.

One has to wonder why these female nurses chose the life courses they did. It is easy to conceive of dutiful Catholic sisters dedicating their professional lives to serving their hospitals and surgeons by providing needed anesthesia services. But what about the others? What made Alice Magaw (1860–1928) enter anesthesia at the Mayo Clinic and reach the high level of skill she did? Much material on her anesthesia achievements is presented but little on *why* she achieved what she did. To be fair, that material may not exist.

A final question is how the AANA developed the political savvy it has. This is an important change from the past. The AANA's ability to achieve such federal legislation as direct reimbursement by Medicare has to be an interesting story, but there is no information given here about *how* the organization matured in that area.

There are extensive quotations of primary material from Thatcher. It would have been useful, for historical accuracy, to verify these primary sources because misquotes and new interpretations of old material may occur. The sources, however, may no longer be available. Although there is a name index, there is no subject index. There are a few typographic errors. The book is a useful addition to the history of nurse anesthesia.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Cane RD, Shapiro BA, Davison RO. *Case Studies in Critical Care Medicine*, 2nd ed. Chicago: Year Book Medical Publishers, 1990, 444 pp, $39.95.

Domino EF, ed. *Status of Ketamine in Anesthesiology*, Ann Arbor, Mich.: NPP Books, 1990, 583 pp, $95.00.

Ferrer-Brechner TR, ed. *Common Problems in Pain Management*, Chicago: Year Book Medical Publishers, 1990, 326 pp, $59.00.

Jones JG, ed. *Depth of Anaesthesia*. Bailliere's Clinical Anaesthesiology Series, Volume 3, No. 3. Philadelphia: Bailliere Tindol, 1989, 242 pp, $22.50.

Kammerer WS, Gross RJ, eds. *Medical Consultation. The Internist on Surgical, Obstetric, and Psychiatric Services*, 2nd ed. Baltimore: Williams & Wilkens, 1990, 676 pp, $59.95.

Marino PL. *The ICU Book*. Philadelphia: Lea and Febiger, 1990, 713 pp, $39.50.

Miranda DR, Williams A, Loriat Ph, eds. *Management of Intensive Care. Guidelines for Better Use of Resources*. Developments in Critical Care Medicine and Anesthesiology, Volume 24. Boston: Kluwer Academic Publishers, 1990, 246 pp, $98.00.

Shapiro BA, Harrison RA, Cane RD, Templin R. *Clinical Application of Blood Gases*, 4th ed. Chicago: Year Book Medical Publishers, 1990, 379 pp, $36.95.

Erratum

Fong J, Gadalla F, Pierri MK, Druzin M. Are Doppler-detected venous emboli during cesarean section air emboli? Vol. 71, No. 3, September 1990, p. 256.

The authors wish to inform readers that the percentage given in the Discussion section (first line of first paragraph and fourth line of last paragraph) should be 29% and not 26%.

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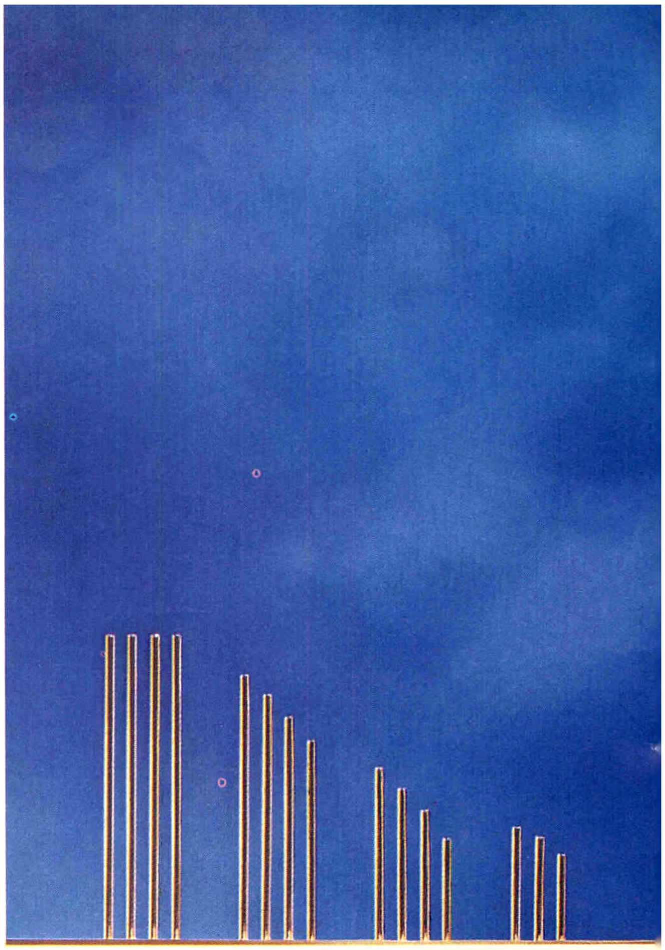

- Excellent alternative to pancuronium[1]
- Unlike pancuronium, free of vagolytic and sympathomimetic effects for enhanced hemodynamic stability[1]
- Good to excellent intubating conditions, 2.5 to 3 minutes

As with other long-acting non-depolarizing neuromuscular blocking agents, ARDUAN® displays a variability in the clinical duration of its effect.

Mean Change From Baseline in Heart Rate, Systolic and Diastolic Blood Pressure

	ARDUAN® 70 mcg/kg		**Pancuronium** 100 mcg/kg	
	Before	2 Min After	Before	2 Min After
Heart Rate (beats/min)	68.9 ± 13.1	72.9 ± 14.1	72.0 ± 15.3	91.4 ± 17.1*
Systolic Blood Pressure (mm Hg)	110.01 ± 18.7	107.0 ± 16.2	107.4 ± 14.4	117.6 ± 14.3*
Diastolic Blood Pressure (mm Hg)	66.0 ± 13.1	64.4 ± 10.4	61.3 ± 12.3	69.0 ± 14.6

*$P < .05$ different from baseline values.

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*Recommended only for procedures 90 minutes or longer.

Reference
1. Data on file.

NEW

ARDUAN®

(pipecuronium bromide) for injection

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NEW
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(pipecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known.
WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.
PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.
Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.
Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.
Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.
Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.
Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.
Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.
Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.
Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.
Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.
Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.
ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:
Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.
Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.
Musculoskeletal: muscle atrophy, difficult intubation.
Nervous: hypesthesia, CNS depression.
Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.
Skin and Appendages: rash, urticaria.
Urogenital System: anuria.
HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bromide and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-37)
Storage: 2°-30°C (36°-86°F). Protect from light.
After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

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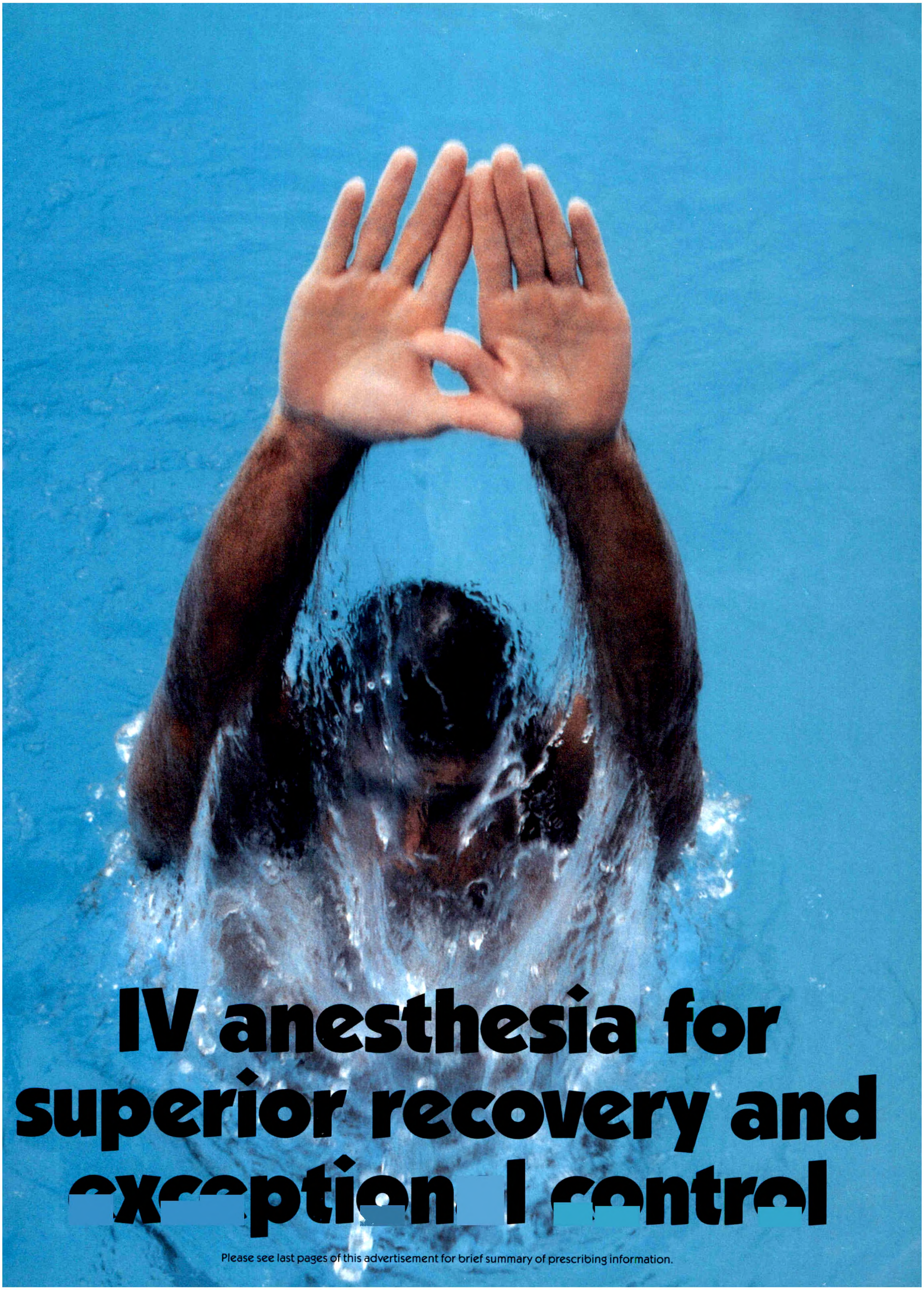

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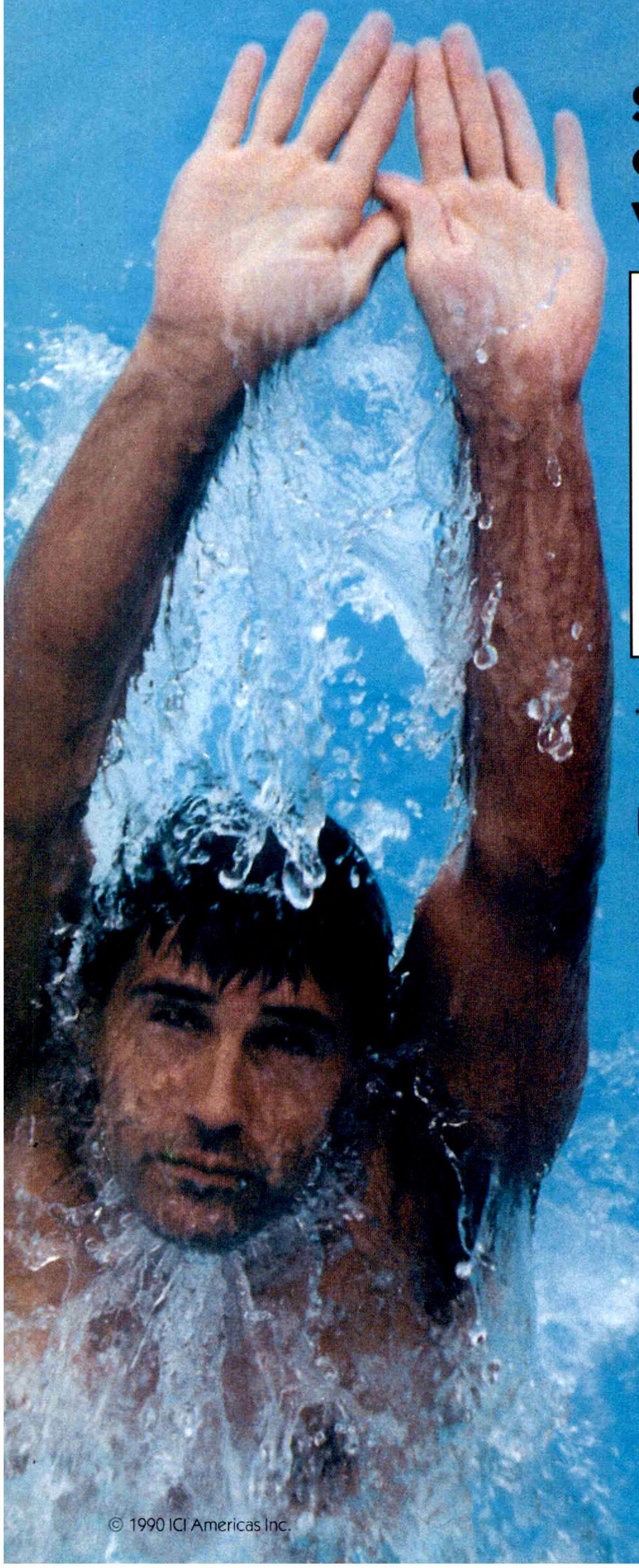

Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- ■ Majority of patients are generally awake, responsive, and oriented within 8 minutes

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ecovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

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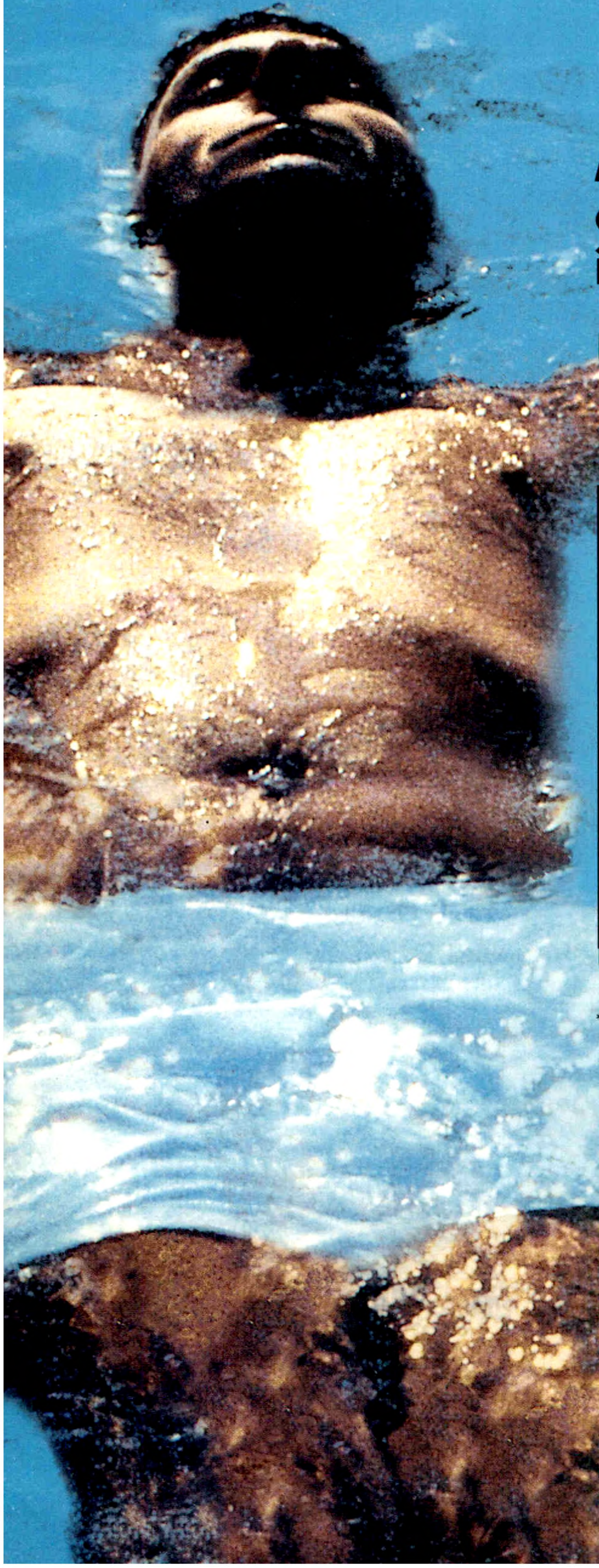
For induction and maintenance

DIPRIVAN®

INJECTION

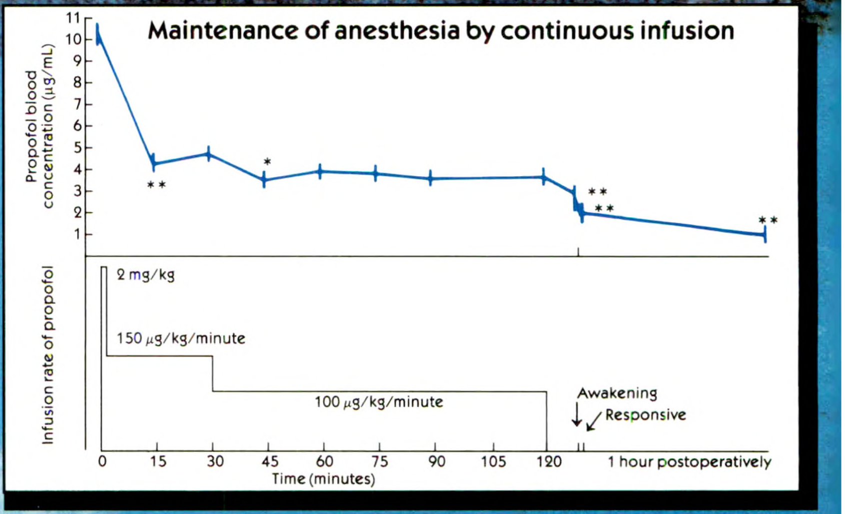
propofol

Superior
exceptional



Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®

INJECTION

propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

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DIPRIVAN®

INJECTION
10 mg/mL
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EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely ($< 1\%$). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae,* in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)*

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

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Manufactured for:
STUART PHARMACEUTICALS
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Classified Advertising

ANESTHESIOLOGY RESIDENCY POSITIONS
Electronic Bulletin Board listing available. Residency positions for CA-1 through CA-3 and fellowship years in anesthesiology. Use telecommunication software on a computer (300 or 1200 baud, 8 data bits, 1 stop bit, no parity) to call (716) 473-4246, answer "yes" to the first question, and then follow the menus. This is a service provided by the Association of Anesthesiology Program Directors and the Department of Anesthesiology at the University of Rochester, Rochester, New York.

424F/L

TENNESSEE
Anesthesiologist: Periodically full-time positions become available at the level of Instructor/Assistant Professor. Applicants must be board certified or in the board process and be interested in resident teaching and clinical research. Tennessee license required. If you would be interested in having your name on file, please reply with curriculum vitae to John T. Chesney, MD, Interim Chairman, Department of Anesthesiology, University of Tennessee Medical Center at Knoxville, 1924 Alcoa Highway, Knoxville, TN 37920. UTMC is an Affirmative Action/Title IX/Section 504 Employer.

436F/L

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity/affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

446G/L

LOUISIANA
Anesthesiologist. Board-certified or -eligible anesthesiologist to fill clinical faculty positions at a University Medical Center. The position responsibilities include administration of anesthesia, teaching of residents, and supervision of CRNAs. Encouragement will be given to initiate or participate in research. Faculty rank and salary will be commensurate with experience. Louisiana State University Medical Center, School of Medicine in Shreveport is an affirmative action/equal opportunity employer. Send curriculum vitae to D. Richard Davis II, MD, Chairman, Department of Anesthesiology, LSU Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932.

468H/A

PACIFIC NORTHWEST
Position available for board certified or soon to be board certified anesthesiologist. Send CV and date available to Box 472H/A.

472H/A

UPSTATE NEW YORK
Full-time anesthesiologists BC or BE to fill available position immediately. Diverse case load. No OH. Pain management experience a plus but not required. Excellent salary and health, life, and disability insurance. Salaried first year leading to early partnership. Send CV and three references to Watertown Anesthesia Services, P.C., P.O. Box 779, Watertown, NY 13601, or call (315) 785-6830.

476H/A

CARDIOTHORACIC ANESTHESIA FELLOWSHIP
Washington University Medical Center. Applications are being accepted for 6- or 12-month fellowship (CA-4) starting in 1991. Full spectrum of adult cardiothoracic anesthesia including arrhythmia surgery, and active heart and lung transplantation program. Research opportunities are available. Address correspondence with CV and names of three references to Demetrios G. Lappas, MD, Director, Division of Cardiothoracic Anesthesia, Washington University Medical Center, 660 South Euclid Campus Box 8054, St. Louis, MO 63110.

483I/L

CALIFORNIA
Los Angeles County, Harbor-UCLA Medical Center, Department of Anesthesiology. Unexpected openings in faculty position at the rank of Assistant Professor. Desire recent graduate of anesthesiology fellowship with research training. Board eligible or certified. Active clinical services, research, and independent residency program in the department. Excellent southern Los Angeles location. Ample academic career opportunities with joint UCLA and LA County appointments. Competitive compensations. Send statement, CV, and list of references to Chingmuh Lee, MD, Professor and Chairman, Department of Anesthesiology, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509. Equal Opportunity Employer.

485I/K

VIRGINIA: CARDIOTHORACIC ANESTHESIOLOGIST
Immediate opening for BC/BE anesthesiologist, with cardiac fellowship training preferred, for a continually growing private adult cardiac anesthesia practice. Currently over 1300 pump cases per year, including EP studies and transplants. Send CV to Box 487I/K.

487I/K

ILLINOIS
Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for two campuses of the only hospital in the city since a recent merger. One facility will provide ophthalmology care; the second will provide ambulatory and in-hospital anesthesia serv-

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

ices. No open heart or neurosurgery. Good opportunity with stable future. Please send CV to Box 488I/K.

488I/K

ANESTHESIOLOGIST

Board-certified or graduating resident to join three BC anesthesiologists. Fee for service. Private, NFP, 117-bed hospital. No craniotomies, OH. Near University of Notre Dame. Reply to Roberta Mann, Medical Staff Services, POB 880, Mishawaka, IN 46544. Telephone (219) 258-1346.

489I/K

REGIONAL ANESTHESIA/PAIN FELLOWSHIP

The Anesthesiology Department at Virginia Mason Medical Center is now accepting applications for the Moore/Bridenbaugh Fellow beginning in July 1991. This position includes a CA3 year in clinical anesthesia followed by a year of research fellowship in regional anesthesia. Contact Stephen M. Rupp, MD, Department of Anesthesia B2-AN, Virginia Mason Medical Center, P.O. Box 900, Seattle, WA 98111.

493I/K

GEORGIA (SOUTH)

Close to Florida and Georgia beaches. Anesthesiologist BC or BE to join corporate group of MDs and CRNAs. First year salary, then partnership. No open heart, no neurosurgery, no routine OB. Full details first letter. Reply to Box 495I/K.

495I/K

ANESTHESIOLOGIST

BC/BE to join the medical staff of a small, rural community hospital. All types of anesthesia. Sport enthusiast's paradise, offering water skiing, fishing, and hunting. Send CV to Administrator, Abrom Kaplan Memorial Hospital, 1310 West 7th Street, Kaplan, LA 70548.

496I/L

FULL-TIME ANESTHESIOLOGIST

BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to 1415 18th Street, Lake Charles, LA 70601.

497I/B

OREGON

Obstetric Anesthesia Fellowship positions for subspecialty training in high-risk obstetrics. Opportunities for clinical and basic research. Send CV, three references, and a summary of career goals to Harvey Carp, MD, PhD, Director of Obstetric Anesthesia, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

499I/K

ILLINOIS

Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad-based practice. All surgical subspecialties represented. Minimal OB and pain management. Early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.

511J/C

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA,

SAN DIEGO is recruiting for four faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol driven human studies. The three other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the four positions may be tenured track. Otherwise the positions are nontenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in Anesthesiology and a California Medical License is required. Possession of a certificate of special qualifications in Critical Care Medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego, is an Equal Opportunity/AA Employer. All applications received by December, 31, 1990 will receive thorough consideration.

518J/L

ATLANTA, GEORGIA: PAIN CONSULTANT

Position available for BC anesthesiologist pain consultant, Pain Management Services, Department of Anesthesiology in 500-bed acute-care hospital. Significant OR anesthesia required as well on a rotating basis. Applicant must have minimum of one year fellowship in pain and have experience in all aspects of acute, chronic, and cancer pain control including proficiency in neural blockade as applied to pain management. Replies with CV to Box 519J/L

519J/L

PEDIATRIC ANESTHESIA FELLOWSHIP

The Department of Anesthesiology, Columbia-Presbyterian Medical Center, is offering a fellowship in pediatric anesthesia at the Babies Hospital. The program is designed for individuals at the CA4, or CA3 and 4 level, who are interested in pursuing academic careers. Interested individuals should contact Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Babies Hospital, BN 440, 622 West 168th Street, New York, NY 10032.

520J/L

MISSOURI

Anesthesiologist, BE/BC needed to join hospital-based group practice in St. Louis area. CRNA supervision required. All specialties except open heart. Excellent salary and fringe benefits package. Send CV to Michael Stelmacki, 1 Insurance Center, Suite 101, Creve Coeur, MO 63141

521J/L

CALIFORNIA

From time to time faculty positions as an Assistant Professor become available in the *Regular Professorial Series (Tenure Track)* in the UCLA Department of Anesthesiology. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills; commitment to discovery; eligibility for a California Medical License; ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

526J/C

CALIFORNIA

Faculty positions in the *Clinician-Teacher* Academic Professorial Series in the UCLA Department of Anesthesiology are available. We are interested in all anesthesia subspecialties. Requisites include eligibility for a California Medical License and ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

527J/C

ANESTHESIOLOGIST/LAUREL, MISSISSIPPI
Join solo anesthesiologist at 275-bed medical center. Community of 20,000 just 90 min from Gulf Coast. Excellent financial package. Interviewing and relocation expenses paid. Send CV or call Greg Pilgrim, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 AAO, Atlanta, GA 30346. Telephone: 1-800-544-1987.

528K

ANESTHESIOLOGISTS, MISSOURI
Anesthesiologists needed at assistant, associate, and professor levels. Must be board certified or board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri-Columbia Health Sciences Center. Interested applicants send Curriculum vitae to G.W.N. Eggers, Jr., MD, Professor and Chairman, Department of Anesthesiology, University of Missouri Health Sciences Center, Columbia, MO 65212.

529K/A

ANESTHESIOLOGIST
Veterans Affairs Medical Center in Grand Junction, Colorado is seeking an anesthesiologist. We offer a competitive salary, 30 days vacation, 13 sick days, 10 paid holidays, retirement including TSP-deferred investment opportunity, health and life insurance, workman's compensation for on-the-job injuries, employee assistance program, and free malpractice insurance. Please call Personnel Service [(303) 242-0731, ext. 2062], 2121 North Avenue, Grand Junction, CO 81501.

530K

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology of Columbus Children's Hospital is expanding its fellowship program. Positions are currently available for a 1-year fellowship in pediatric anesthesiology. Children's Hospital of Columbus, Ohio is a 313-bed general pediatric institution with a surgery caseload of 13,000–14,000 cases per year. All pediatric surgical specialities are represented with large case loads in pediatric neurosurgery and cardiovascular surgery. Regional anesthesia in infants and children along with acute/chronic pain management experience is available. An active transplantation service is present. Opportunity for research is provided under the guidance of a full-time director of research. Inquiries should be submitted to J. David Martino, MD, Chairman, Department of Anesthesiology, Columbus Children's Hospital, Columbus, OH 43205.

531K/D

GEORGIA
BC/BE anesthesiologist needed to join private practice in the Atlanta area. Position available for July 1991. No hearts. Send CV to WS, 31 Hanarry Drive, Lawrenceville, GA 30245 or (404) 995-4680.

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ATLANTA, ANESTHESIOLOGIST
Needed to join one doctor and three CRNAs in this suburban community hospital. State-of-the-art department with low stress environment. No neuro, no hearts. Send CV or call: MCM Anesthesia, 1311 Crestline Drive, Smyrna, GA 30080: (404) 920-6300.

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OHIO
University of Cincinnati, Department of Anesthesia, has faculty positions at assistant/associate professor levels. Candidates should be board eligible/certified and eligible for licensure in the state of Ohio. Applicants with interest in neuroanesthesia, cardiac anesthesia, and regional anesthesia are encouraged to apply. We are an equal opportunity/affirmative action employer. Send curriculum vitae and references to Phillip O. Bridenbaugh, MD, Chairman, Department of Anesthesia, University of Cincinnati College of Medicine, 231 Bethesda Avenue, Cincinnati, OH 45267-0531.

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The Alfred I. duPont Institute is an expanding, 100-bed children's hospital located on a 300-acre estate just northwest of Wilmington, Delaware and 30 minutes south of Philadelphia. For more information, please send your curriculum vitae to Robert G. Kettrick, MD, Director, Departments of Anesthesiology and Critical Care, Alfred I. duPont Institute, P.O. Box 269, 1600 Rockland Road, Wilmington, DE 19899.

537K

FELLOWSHIP AND CA-3
(Positions in Pain Management)
The Pain Management Center at The Cleveland Clinic Foundation has positions available for those interested in advanced training in acute and chronic pain management. A large multidisciplinary program for inpatients and outpatients provides care for a wide range of chronic pain states. The Pain Center is integrated with the Spine Center, a well-established Drug Dependency Unit in the Department of Psychiatry, and the Cancer Center. Fellows are encouraged to spend a varying amount of their training in these three areas. In addition to the usual experience obtained from the medical management, regional anesthetic, and neurologic procedures, as well as long-term indwelling catheter systems, being a referral center for the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA), a large exposure to patients suffering from sympathetically maintained pain states will be gained. Fellows are expected to participate and CA-3 residents will be given the opportunity to undertake research on the acute and chronic pain services. Twelve-month fellowships are available for residents having successfully completed a CA-3 year, as are CA-3 programs of 6 or 12 months. Inquiries may be directed to Michael Stanton-Hicks, MB, BS, MD, Director, Pain Management Center, M-60, Department of Anesthesiology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195-5254. Telephone: (216) 444-3769.

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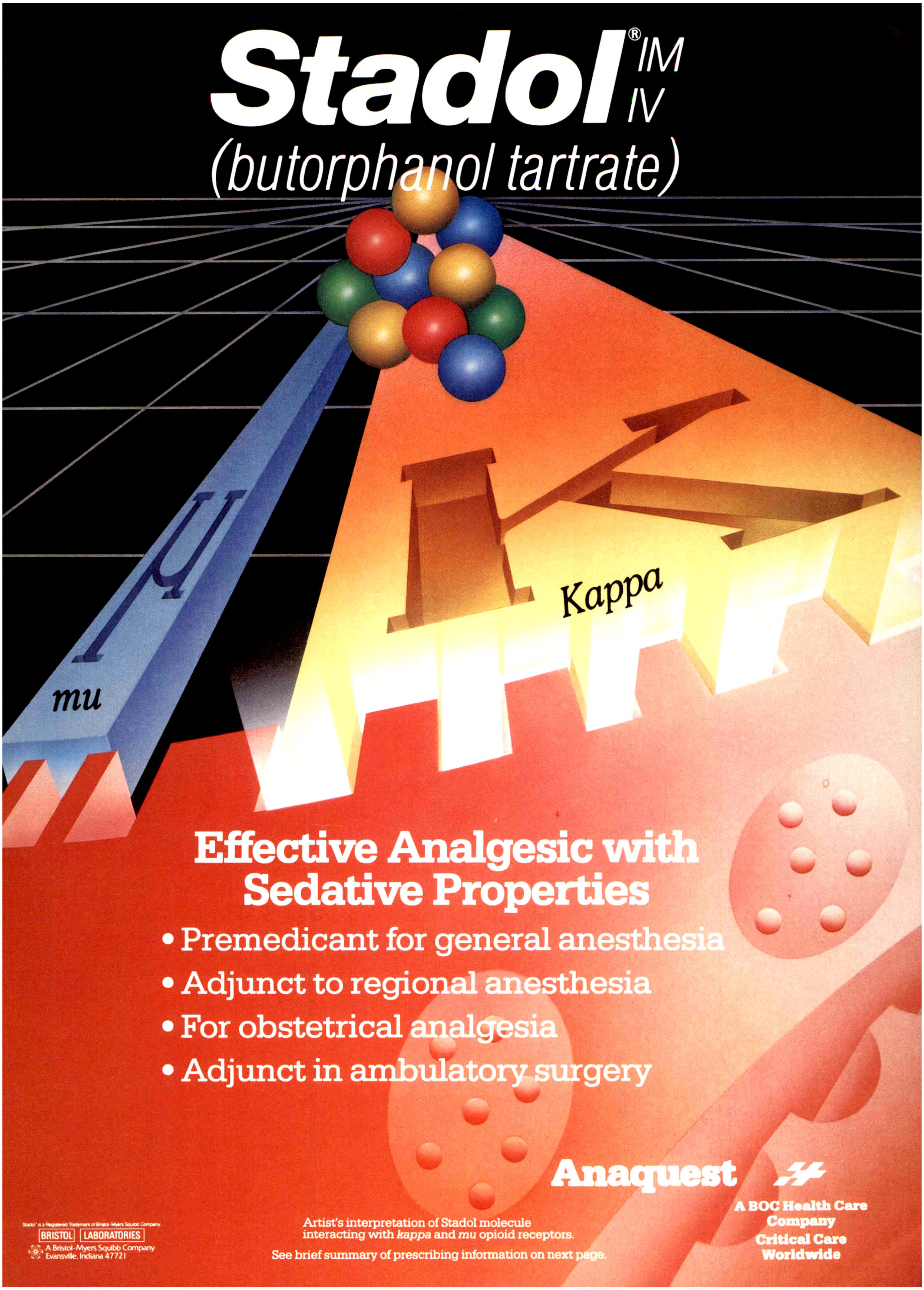
WASHINGTON
Anesthesiologists, BC/BE: need one now and two in spring to join group of 15 MDs. Must be proficient in cardiac, neuro, OB, and with pain experience. Located on Puget Sound. Unusually equitable salary and benefits. Send CV to John Meisburger,



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Artist's interpretation of Stadol molecule interacting with *kappa* and *mu* opioid receptors.

See brief summary of prescribing information on next page.

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Stadol® *(butorphanol tartrate)*

For complete information consult official package circular.

INDICATIONS AND USAGE
Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS
Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS
Patients Physically Dependent on Narcotics
Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia
Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence
Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure
Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects
Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS
Certain Respiratory Conditions
Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function
Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery
Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication
Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy
The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human does.

Usage in Labor and Delivery
In general, the safety to the mother and fetus following the administration of Stadol during labor has been established, however, there have been a few reports of infant respiratory distress/apnea occurring after delivery (less than 1%; see Adverse Reactions). Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers
The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children
Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS
The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (36, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (16, 1%), lightheadedness (12, 1%).

Other adverse reactions may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: Vomiting

Respiratory: slowing of respiration, shallow breathing, apnea

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE
Manifestations
Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment
The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY
Stadol (butorphanol tartrate Inj., USP) for I.M. or I.V. use is available as follows:
NDC 0015-5644-20 - 2 mg per mL, 2-mL vial
NDC 0015-5645-20 - 1 mg per mL, 1-mL vial
NDC 0015-5646-20 - 2 mg per mL, 1-mL vial
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For information on package sizes available, refer to the current price schedule.

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ANESTHESIOLOGIST

West Virginia University (WVU) Health Sciences Center, Department of Anesthesiology, is recruiting for an anesthesiologist. Our Department currently has 15 faculty members and sponsors an approved residency training program, which has 24 residents.

Requirements for entry as Assistant Professor include completion of CA III or fellowship year, with Board Certification preferred. An outstanding teaching opportunity is provided as resident and medical student education represent the primary mission of the Department. Consideration for either a research or a clinical track will be based on candidate background and preference. Interest in anesthesia for pediatrics, obstetrics, neurosurgery, and pain management is desirable.

WVU is in Morgantown, West Virginia, approximately 75 miles south of Pittsburgh on major interstate highways. The area, providing abundant recreation for all seasons, is situated in the scenic Allegheny Highlands region.

Clinical services are provided at the Ruby Memorial Hospital, a tertiary care center which opened in July, 1988. This $87 million, 376-bed facility features 12 operating rooms, all with state-of-the-art equipment.

As evidence of tremendous institutional growth is the new $25 million Physician Office Center, which houses the largest multi-specialty group practice in the State; the new Cancer Center, which is the State's only NCI-designated cancer research center; Chestnut Ridge Hospital, a 70-bed psychiatric hospital for comprehensive inpatient and outpatient care; and a 60-bed rehabilitation hospital, now under construction.

WVU is an Equal Opportunity/Affirmative Action Institution.

For additional information, contact: Edward Stullken, M.D., Chairman, Department of Anesthesiology, WVU Health Sciences Center, Morgantown, WV 26506. Telephone: (304) 293-5411.

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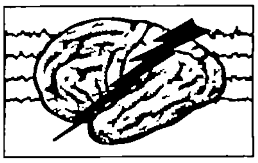

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Course tuition is $500 ($550 after November 30, 1990). Cancellation of registration by written notification only prior to December 1, 1990. There is a $50 cancellation fee. This program has been approved for 25 hours in Category 1 of the Physicians Recognition Award of the American Medical Association.

For complete information contact Mrs. Carolyn Schoenau, Program Coordinator, Anesthesiology Alumni Association of Florida, Inc., Post Office Box 13417, Gainesville, Florida 32604 (Area code 904 392-8959).

MD, St. Joseph Hospital, Department of Anesthesia, 1718 South I Street, Tacoma, WA 98405-5051.

540K

CALIFORNIA
Anesthesiology, Pain Management Fellowship, UC Irvine. The University of California, Irvine, Department of Anesthesiology is accepting applications for CA4 fellowship positions in Pain Management. The rapidly expanding Pain Management Center at UC Irvine offers extensive clinical experience and education in all aspects of acute and chronic pain. With the addition of six new Pain Management faculty, there is extensive emphasis on the teaching of regional anesthetic techniques, invasive and noninvasive chronic pain regimens, and involvement of other disciplines. The clinic for chronic pain provides services to all types of pain patients, and the large University Medical Center is an excellent medium for the use of standard and sophisticated acute pain modalities. In addition to developing clinical expertise in pain management, our fellows get involved in research projects with the help of a full-time research assistant. Six-month or one-year fellowships are available. MD degree and California license are required. Send curriculum vitae and three references to Carl A. Hess, MD, Director, Pain Management Center, Department of Anesthesiology, University of California, Irvine, 101 City Drive South, Route 81A, Orange, CA 92668; (714) 634-6437. The University of California, Irvine is an equal opportunity employer.

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ISSN 0003-2999
Volume 71, Number 6, December 1990

(82)

Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

The Logical Choice

Critical Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection	**atracurium besylate**
HEMODYNAMICS	Virtually free of cardiovascular side effects, even at higher doses (0.28 mg/kg)[1]	Significant variations in blood pressure and cardiac output[2]
HISTAMINE	Histamine release unlikely even at 0.28 mg/kg	Precaution advised for patients in whom substantial histamine release would be hazardous (clinically significant cardiovascular disease, asthma)[3]
DURATION OF ACTION	Shorter-acting at equipotent doses[4]	Significantly slower recovery[4]
DOSING FLEXIBILITY	Can be used in short, intermediate, or long cases. No dosage adjustments required to avoid cardiovascular side effects[5]	Doses higher than 0.5 mg/kg not recommended.[3] Dosage adjustments needed to avoid histamine release[3,6]
STORAGE	Room temperature	Constant refrigeration[3]
STABILITY	2-year shelf life in lyophilized form	2-year shelf life (under refrigeration) immediately reduced to 14 days once removed from refrigeration, even if re-refrigerated[3]

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.

Norcuron
(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.
WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.
PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.
Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.
Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.
Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.
Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.
Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.
Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.
C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.
Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.
Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.
Drug/Laboratory test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.
Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.
Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.
ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.
OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.
DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenou bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-3 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% o control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after th start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. Howev clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for ea patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascula system being noted as long as ventilation is properly maintained.
Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initi approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recove from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Avera infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5 glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pun

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug μg/kg/min	Patient Weight – kg 40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial do and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 we are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. S also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in chi therefore, no dosing recommendation can be made.
COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution	5% glucose in saline
5% glucose in water	Lactated Ringers
Sterile water for injection	

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
STORAGE: 15-30°C (59-86°F). Protect from light.
AFTER RECONSTITUTION:
- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 ho Single use only. Discard unused portion.

REV.

References:
1. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery byp grafting. *Anesthesiology*. 1983;58:438–440.
2. Gallo JA, Cork RC, Puchi P. Comparison of effects of atracurium and vecuronium in cardiac surg patients. *Anesth Analg*. 1988;67:161–165.
3. Tracrium* Injection (atracurium besylate) package insert.
4. Bailey DM, Nicholas ADG. Comparison of atracurium and vecuronium during anaesthesia for laparoscopy. *Br J Anaesth*. 1988;61:557–559.
5. Feldman SA. Vecuronium — A variable dose technique. *Anaesthesia*. 1987;42:199–201.
6. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anaesth*. 1985;57:550–553.

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Anesthesia and Analgesia

Journal of International Anesthesia Research Society

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As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Predictable control of stress responses from induction through recovery

***REDUCES** stress response to intubation and surgical stimulation* [1,2]

***PROVIDES** intraoperative hemodynamic stability*

***CONTROL** of the stress response is associated with less postoperative morbidity* [3,4]

***MAINTAINS** postoperative analgesia with faster recovery of respiratory drive* [5]

*References: **1.** de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. **2.** Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. **3.** Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. **4.** Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. **5.** Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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March 1986, March 1987
U.S Patent No. 3,998,834
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Anesthesia and Analgesia

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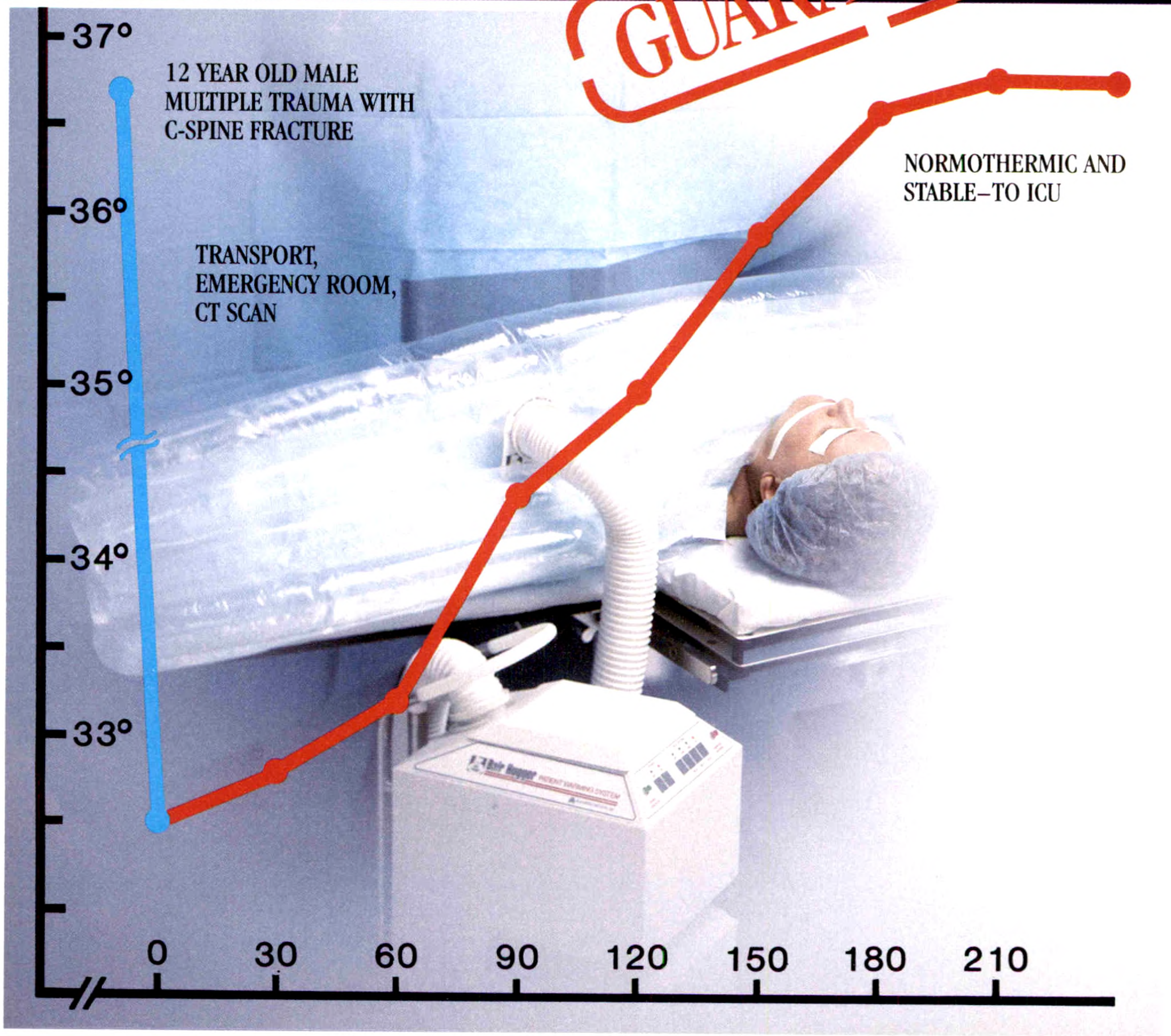

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CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of $\geq$ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses $\leq$ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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1. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology.* 1984;61:444-453.
2. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172.
3. Lawson DH, Paice GM, Glavin RJ, et al. Atracurium — a post-marketing surveillance study: U.K. study and discussion. *Br J Anaesth.* 1989;62:596-600.

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For additional information, contact: Edward Stullken, M.D., Chairman, Department of Anesthesiology, WVU Health Sciences Center, Morgantown, WV 26506. Telephone: (304) 293-5411.

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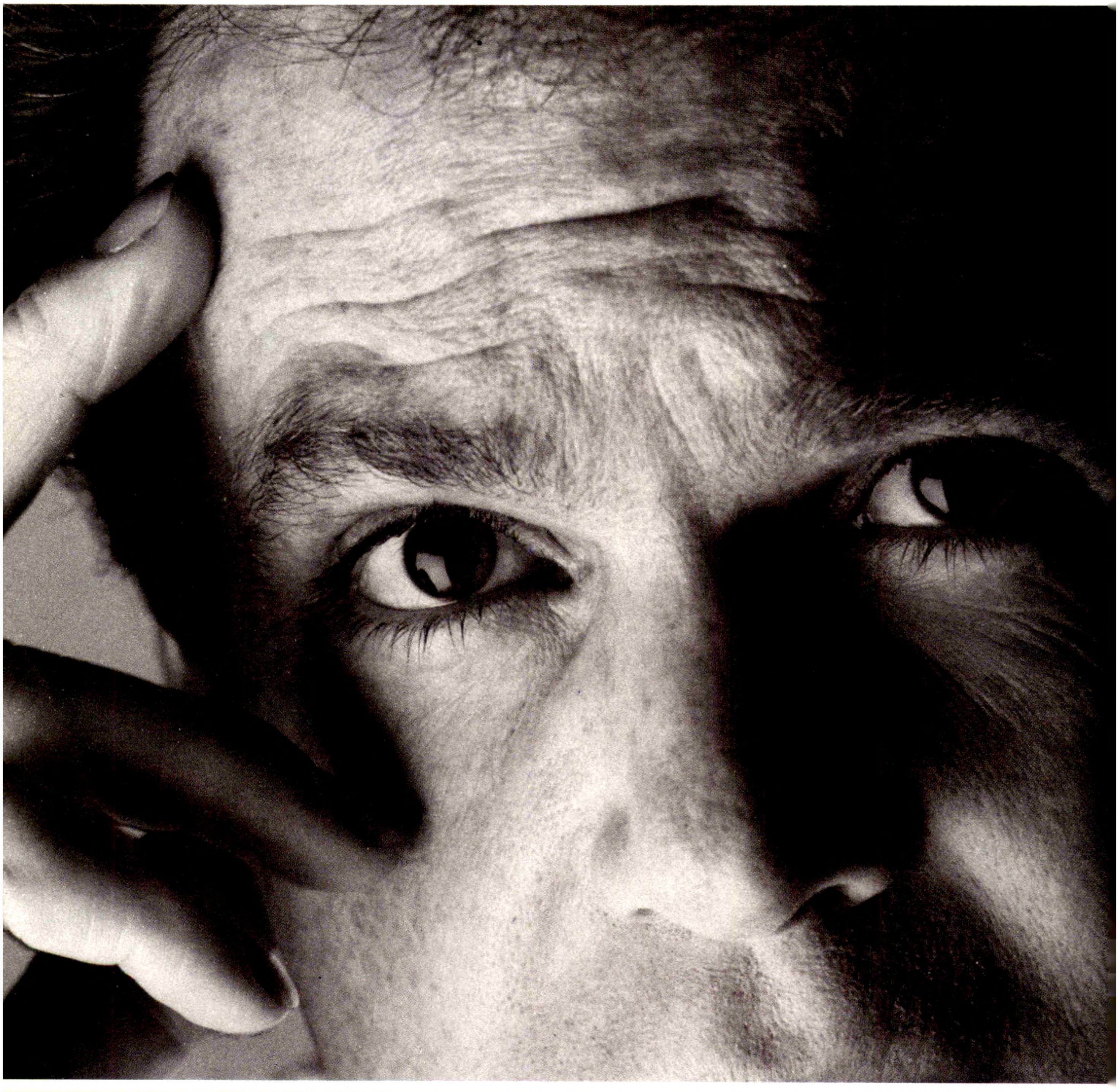

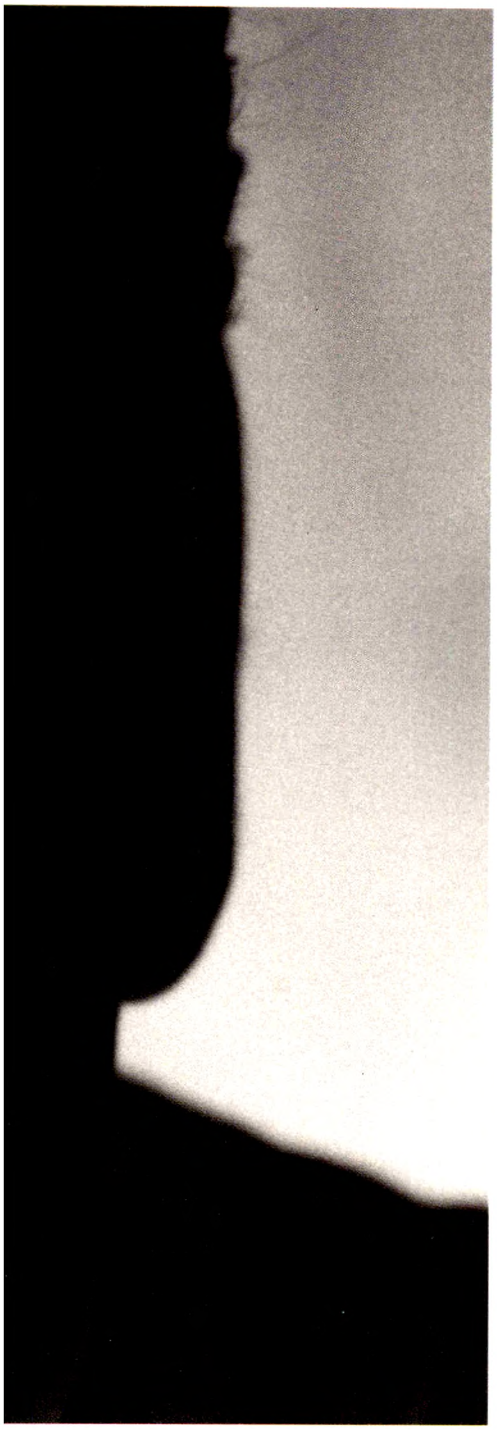

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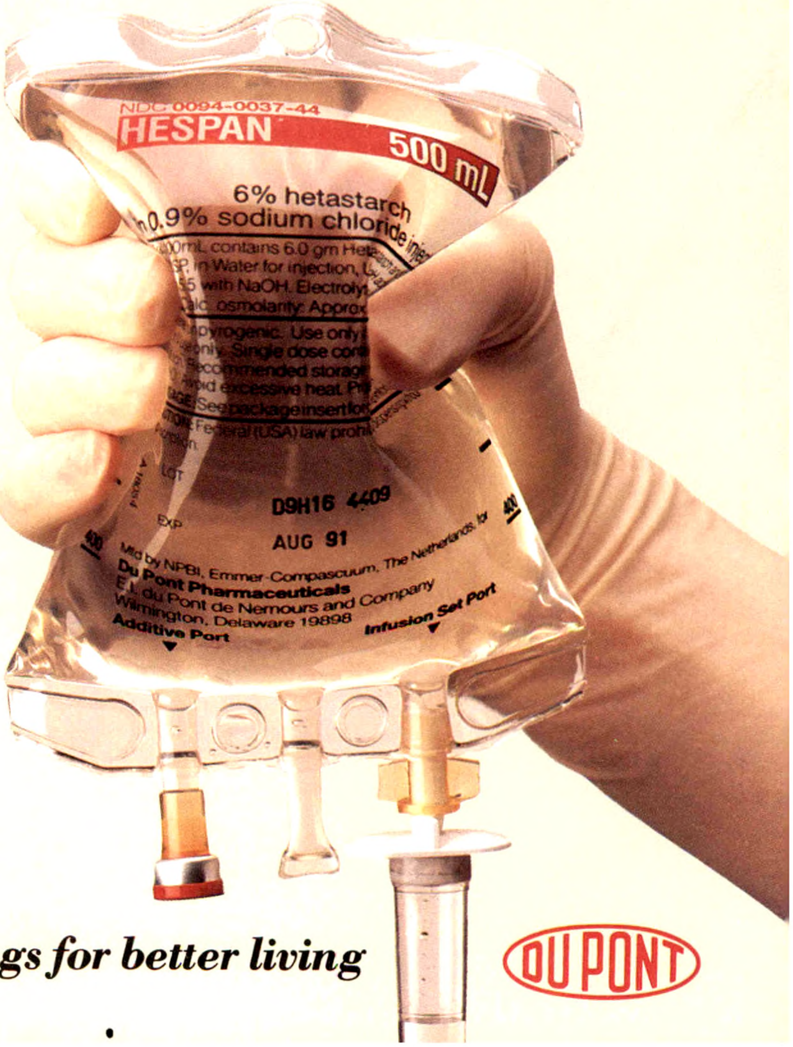

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References: 1. Hespan® Prescribing Information. **2.** Waters LM, Christensen MA, Sato RM: Hetastarch: An alternative colloid in burn shock management. *J Burn Care Rehabil* 1989;10:11–16. **3.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983;11:839–850.

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CONTRAINDICATIONS

HESPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. HESPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS

Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing) bleeding due to hemodilution (see Warnings), and circulatory overload and pulmonary edema (see Precautions).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis

250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The safety and compatibility of other additives have not been established.

HOW SUPPLIED

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

HESPAN is supplied sterile and nonpyrogenic in 500 mL intravenous plastic infusion containers (NDC 0056-0037-44) and 500 mL intravenous glass bottles (NDC 0056-0037-05).

CAUTION

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The **American Board of Anesthesiology (ABA)** will administer its fourth written examination in **CRITICAL CARE MEDICINE** at the Westin Hotel-O'Hare in Rosemont, Illinois on Friday, September 27, 1991. Diplomates of the ABA and other ABMS Member Boards who apply and are judged to be qualified by virtue of their additional training or experience in Critical Care Medicine will be accepted for examination. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 100 Constitution Plaza, Hartford, Connecticut 06103-1721. The deadline for receipt of completed applications in the Board office is April 30, 1991.

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Clinical Pharmacology of Nitrous Oxide: An Argument for Its Continued Use

Edmond I. Eger II, MD, George H. Lampe, MD, Linda Z. Wauk, RN,
Patricia Whitendale, RN, Michael K. Cahalan, MD, and Judith H. Donegan, MD, PhD

EGER EI II, LAMPE GH, WAUK LZ, WHITENDALE P, CAHALAN MK, DONEGAN JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85.

We tested the hypothesis that the administration of nitrous oxide (N_2O) causes major (e.g., myocardial infarction, neuronal injury, hypoxemia, infection, death) or minor (e.g., nausea, vomiting, headache, earache) untoward effects in patients requiring anesthesia for 1.5–4 h. Given the higher morbidity and mortality associated with aging, we also tested whether aging increased any untoward effect of N_2O. Finally, we investigated whether the substitution of N_2O for a fraction of the anesthesia supplied by isoflurane altered the latter's pharmacologic effects. We studied 270 patients scheduled for elective total hip arthroplasty (n = 100), carotid endarterectomy (n = 70), or transsphenoidal hypophysectomy (n = 100) who were randomly assigned within each surgical group to receive isoflurane with or without 60% N_2O. Regardless of patient age, we found no difference in major or minor untoward outcomes between anesthetic groups, nor a trend to suggest that a larger data cohort would reveal a significant adverse effect of N_2O. The addition of N_2O administration decreased the isoflurane requirement for clinical anesthesia but did not alter most of the clinical variables measured in practice, including blood pressure, heart rate, rate of recovery from anesthesia, development of postoperative pain, patient satisfaction with anesthesia, or duration of anesthesia or of hospitalization. Patients given N_2O were no more likely to dream during anesthesia, remember events during anesthesia, or be frightened by those events. Our results support the continued use of N_2O to anesthetize patients for elective surgery.

Key Words: ANESTHETICS, GASES—nitrous oxide.

Nitrous oxide (N_2O) possesses many of the attributes of the ideal anesthetic (1,2). Low solubility and the consequent kinetic benefits are complemented by a stability of respiration and circulation. It is an easily breathed, inexpensive gas that has a long history of apparently safe and effective use. It is our "gold standard" for analgesia produced with inhaled agents.

However, N_2O is not the ideal anesthetic (3). It cannot be used effectively without decreasing the concentration of oxygen that may be delivered. Undesirable kinetic properties may harmfully expand internal gas spaces. Such expansion may distend the intestine, impair operating conditions, and prolong hospitalization (4). Nitrous oxide can depress respiration and circulation (3), particularly in patients with initially compromised function. It increases muscle tone, thereby increasing the dose requirement for muscle relaxants. It increases cerebral blood flow and intracranial pressure and, unlike other inhaled anesthetics, does not protect the brain by decreasing cerebral oxygen consumption. Like oxygen, it supports combustion.

Finally, and most importantly, N_2O has the capacity to produce permanent injury by inactivating the vitamin B_{12} component of the enzyme methionine synthase. Results from laboratory, epidemiologic, and anecdotal reports indicate that this action may produce noxious, perhaps toxic, effects (5,6). The prolonged use of N_2O (i.e., for days) can cause aplastic anemia and death (7). Repeated exposures or abuse of N_2O can cause neuronal degeneration (8). Prolonged inhalation of very small concentrations may injure the liver, kidney, brain, and peripheral nerves, and the fetus of a pregnant woman (9). Acute exposure of critically ill patients to N_2O may produce megaloblastic changes and death (10).

Supported in part by PO1 AG03104A, the Anesthesia Research Foundation, and a grant from Anaquest, Inc.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication June 27, 1990.

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However, most of the available evidence does not apply to the ordinary patient undergoing anesthesia and surgery of moderate duration. Anecdotal reports of injury in this population are inadequate, given the ubiquitous use of this agent. Because its use is ubiquitous, no large comparison groups are available, and thus it is difficult to determine whether injury is independent of or due to the administration of N_2O. The few prospective randomized studies comparing the effects of anesthesia with and without N_2O are limited in scope, usually revealing no noxious effect (e.g., see Cahalan et al. [11]), or reported only minor changes (e.g., atrioventricular dissociation [12]). One exception is the recent report by Scheinin et al., who found that N_2O administration prolonged hospitalization in patients having bowel surgery (4).

Finally, studies in volunteers suggest that the pharmacologies of N_2O and other inhaled agents differ or that the addition of N_2O alters the pharmacology of other inhaled agents. Given alone to volunteers at anesthetizing partial pressures, or in combination with isoflurane, N_2O increases blood pressure and heart rate (13,14), effects that are not apparent in clinical practice.

These considerations led us to an evaluation of the clinical pharmacology of N_2O and a measurement of the incidence and type of adverse outcomes in surgical patients exposed to clinically relevant concentrations for 1.5–4 h. The present report, and the seven reports that immediately follow, emerged from this evaluation. The present report focuses on the clinical perioperative effects of N_2O and gives an overview of the influence of N_2O on morbidity and mortality. In part, this overview summarizes the detailed results presented in the subsequent reports. For example, these reports explore the potential of N_2O to produce untoward effects on myocardial, hepatic, pulmonary, and hematopoietic tissues; the present report summarizes these data and adds information on the potential of N_2O to affect the brain adversely and to produce unwanted effects such as nausea. In addition, we offer data on analgesia, awareness, recovery from anesthesia, and simple hemodynamic effects of N_2O.

Methods

We studied 270 patients scheduled for elective total hip arthroplasty (*n* = 100), carotid endarterectomy (*n* = 70), or transsphenoidal hypophysectomy (*n* = 100) after they consented to participate in our institutionally approved study. All data collection, analysis, and patient interviews were performed by medical personnel blinded to the anesthetic regimen. We collected preoperative historical data, including cardiorespiratory and neurologic disease status, hepatic and renal disease status, medication history, and smoking habits. Preoperatively, we asked all patients to report their experience of any of 18 common symptoms (Table 1) over the week preceding surgery and, postoperatively, to identify changes in symptoms during the first 24 h, and at 48 and 72 h.

All patients received isoflurane, thiopental, and vecuronium, but were randomly assigned to receive 60% N_2O/40% O_2 (*n* = 133) or 100% O_2 (*n* = 137). The concentration of isoflurane was determined by the attending anesthesiologist. Patients having total hip replacement also received either a spinal (*n* = 92) or an epidural (*n* = 8) anesthetic. Fentanyl and edrophonium/atropine were administered at the anesthesiologist's discretion.

After intubation, a heat-and-moisture exchanger (Humid-vent) was placed at the end of the endotracheal tube of all patients. Ventilation was controlled, and total gas flows of 5 L/min were maintained throughout surgery. Tidal volume was 10–15 mL/kg, and the respiratory rate was adjusted to maintain P_{ETCO_2} at approximately 30–35 mm Hg. Patients having carotid endarterectomy also were monitored with transesophageal echocardiography, continuous electrocardiography (Holter monitoring), and, in some cases, serial measurement of creatine kinase-MB levels. The data for the results from these measurements are reported in detail in a companion paper in this series (15).

The operative period was divided into three intervals during which drug dosage and physiologic variables were measured: (a) induction to 10 min, (b) 10–60 min, and (c) >60 min. Median dialed (delivered) and end-tidal concentrations of isoflurane were recorded for these periods. Isoflurane, N_2O, and P_{ETCO_2} were measured by mass spectroscopy.

Heart rate and systolic blood pressure values were recorded by nursing personnel during the 24 h preceding surgery, and the lowest value for each was used as the baseline value for all but those patients having carotid endarterectomies, for whom we used the median values. These values were then measured at least every 5 min intraoperatively and every 15 min in the recovery room (using a Dynamap recorder) to determine their median, lowest, and highest values. Esophageal (operating) or axillary (recovery room) temperatures were recorded throughout anesthesia and the recovery period. We recorded the duration of anesthesia and hospitalization.

We obtained a "pain score" at 15, 30, 60, and 90 min after admission to the recovery room: 0 = patient

Table 1. Questionnaire: Symptoms and Signs Elicited Preoperatively and Postoperatively

	Preoperatively	First 24 h	Day 1	Day 2	Days 5–7
Total numbers					
N_2O	133	126	126	125	39
No N_2O	137	134	134	132	41
Cough					
N_2O	36 (27)	38 (30)	25 (20)	29 (23)	4 (10)
No N_2O	32 (23)	52 (39)	30 (22)	29 (22)	5 (12)
Headache					
N_2O	55 (41)	81 (60)	46 (36)	46 (37)	9 (23)
No N_2O	54 (39)	79 (63)	47 (35)	49 (37)	14 (34)
Vomiting					
N_2O	7 (5)	58 (46)[a]	3 (2)	0 (0)	0 (0)
No N_2O	4 (3)	46 (34)	5 (4)	4 (3)	0 (0)
Constipation					
N_2O	25 (19)	15 (12)	14 (11)	21 (17)	8 (21)
No N_2O	31 (23)	11 (8)	14 (10)	29 (22)	10 (24)
Numbness or tingling					
N_2O	30 (23)	29 (23)	24 (19)	25 (20)	11 (28)
No N_2O	27 (20)	32 (24)	24 (18)	29 (22)	16 (39)
Chest pain (angina)					
N_2O	5 (4)	1 (1)	0 (0)	1 (1)	0 (0)
No N_2O	1 (1)	2 (2)	0 (0)	2 (2)	1 (2)
Coughing up mucus					
N_2O	23 (17)	41 (33)	20 (16)	36 (29)	6 (15)
No N_2O	21 (15)	43 (32)	23 (17)	31 (23)	4 (10)
Trouble concentrating					
N_2O	29 (22)	34 (27)	23 (18)	26 (21)	9 (23)
No N_2O	28 (20)	46 (34)	36 (27)	24 (18)	8 (20)
Weakness, lack of energy					
N_2O	53 (40)	82 (65)	68 (54)	68 (54)	21 (54)
No N_2O	52 (38)	78 (58)	69 (51)	65 (49)	20 (49)
Upset stomach, nausea					
N_2O	25 (19)	60 (48)	13 (10)	14 (11)	2 (5)
No N_2O	20 (15)	62 (46)	17 (13)	15 (11)	6 (15)
Dizziness, feel faint					
N_2O	22 (17)	34 (27)	12 (10)	11 (9)	7 (18)
No N_2O	23 (17)	33 (25)	14 (10)	14 (11)	8 (20)
Drowsiness (day)					
N_2O	55 (41)	100 (79)	81 (64)	67 (54)	19 (49)
No N_2O	64 (47)	108 (81)	90 (67)	83 (63)	24 (59)
Muscle pains, cramps					
N_2O	42 (32)	25 (20)	17 (13)	19 (15)	7 (18)
No N_2O	37 (27)	30 (22)	18 (13)	15 (11)	9 (22)
Sore throat					
N_2O	13 (10)	62 (49)	51 (40)	42 (34)	4 (10)
No N_2O	18 (13)	60 (45)	55 (41)	42 (32)	3 (7)
Unhappiness, sadness					
N_2O	41 (31)	17 (13)	13 (10)	18 (14)	5 (13)
No N_2O	38 (28)	16 (12)	8 (6)	15 (11)	5 (12)
Difficulty urinating					
N_2O	6 (5)	47 (37)	34 (27)	23 (18)	2 (5)
No N_2O	5 (4)	47 (35)	32 (24)	20 (15)	1 (2)
Earache					
N_2O	5 (4)	10 (8)	3 (2)	5 (4)	2 (5)
No N_2O	6 (4)	7 (5)	6 (4)	4 (3)	0 (0)
Stuffy nose					
N_2O	29 (22)	69 (55)	66 (52)	55 (44)	10 (26)[b]
No N_2O	43 (31)	73 (54)	67 (50)	59 (45)	19 (46)

N_2O, nitrous oxide.

Values are expressed as the number of patients responding affirmatively; percentages are given in parentheses.

[a] $P = 0.059$ compared with the no-N_2O value (Fisher's exact test, two-tailed).

[b] $P = 0.066$ compared with the no-N_2O value (Fisher's exact test, two-tailed).

is unresponsive; 1 = patient reports no pain; 2 = little pain; 3 = a lot of pain; and 4 = unbearable pain. We simultaneously assessed the patient's orientation to place. At 90 min, we asked each patient: "Did you dream during anesthesia?" We recorded the time from the end of anesthesia to the first administration of narcotic, and the time spent in the recovery room.

For the first 7 days after anesthesia, we recorded the highest oral temperature occurring in each 8-h shift. We obtained hematocrit and white blood cell values when surgeons obtained these data, and recorded the highest and lowest postoperative white blood cell count and sampling date. On postoperative day 2, we asked all patients to rate their satisfaction with the anesthetic on a scale from 1 (completely satisfied) to 4 (completely dissatisfied), and to specify any memory of events during anesthesia, in particular any frightening ones.

We recorded the following data in all patients for postoperative days 0, 1, 2, and >2: hypoxemia (oxygen saturation <86%); suspected infection (temperature >38°C for two consecutive 8-h shifts and a white blood cell count >13,000); bacteremia (a positive blood culture taken when infection was suspected); wound infection (determined by the surgeon in the setting of suspected infection); and urinary tract infection ($>10^6$ colonies of organisms/mL) in the setting of suspected infection. We recorded the presence of atelectasis, pneumonia, pulmonary edema, or pneumothorax in hypoxemic patients requiring a chest x-ray (reviewed by a radiologist to evaluate outcome). The evidence for pulmonary dysfunction is reported completely in a companion paper (16). We also sought evidence for myocardial infarction (new abnormalities in postoperative creatine kinase isoenzymes or Q-wave development) in patients having carotid endarterectomies. In patients having total hip arthroplasties, we sought evidence for hepatic injury (increases in alanine aminotransferase to abnormal levels). Details of these studies are reported separately (15,17). We recorded the number of patients requiring reoperation within 24 h after their initial surgery, and the number of deaths in the hospital after surgery.

Patients were interviewed preoperatively and postoperatively to evaluate untoward effects and neuropsychologic function. We interviewed all patients by symptom questionnaire (Table 1) and required all to take both forms (forward and backward) of the digit-span test. Each patient was asked to repeat numbers spoken by the interviewer. The numbers were randomly sequenced in successively larger sets (e.g., "5,3,9" "2,7,6,1"). If a set was repeated incorrectly, a set of the same size containing different numbers was used, and, if again incorrect, testing was ended. The largest set correctly repeated became the score. The backward form differed only in requiring patients to repeat the numbers in reverse order.

For patients having carotid endarterectomies, we recorded cooperation during the preoperative and postoperative interviews, and an orientation score obtained by asking three questions: name, city in which hospitalized, and day of week. Correct replies gave a total score of 3 (1 per item).

Evaluations of neurologic function were obtained in subsets of the patients having total hip replacements or carotid endarterectomies (patients enrolled after the study was about half completed; $n = 71$). We obtained the Glasgow Coma Score preoperatively and on postoperative days 1, 2, and 5, 6, or 7. Simultaneously, we examined these patients for peripheral neuropathy affecting the ulnar, median, radial, peroneal, and tibial nerves. Each nerve was tested for motor function and for perception of position, pinprick, and cold. Accordingly, the total score ("yes" or "no" for the presence of function) bilaterally for all nerves was 40. Patients having carotid endarterectomy also were tested for neurologic deficits (contralateral weakness or numbness; dysphasia or confusion; blurring of vision; and homonymous visual field loss).

Data were analyzed using *t*-tests, Fisher's exact test (two-tailed), and χ^2 analyses to compare the results from the two anesthetic groups, and by regression analyses to define the effect of age and any interaction of aging and N_2O. We also analyzed the data within each surgical group to assess whether one operation might predispose to changes that were obscured when data from all groups were combined.

The pharmacologic, hemodynamic, and outcome variables examined in this study were chosen a priori as variables potentially affected by N_2O use. We recognized the potential for type I (α) errors associated with multiple comparisons, and established a priority scale for identifying selected variables and outcomes as secondary (of lesser importance) and therefore subject to more stringent statistical criteria for significant change. However, these criteria were not required because so few differences were found!

Results

Demographic factors (Table 2) and anesthetic management (Table 3) did not differ between groups, except that patients anesthetized without N_2O were given higher concentrations of isoflurane. However, the total anesthetic dose, as defined by MAC multi-

Table 2. Patient Demographic (Preoperative) Characteristics

	N_2O	No N_2O
n	133	137
Age (yr)	54 ± 18	54 ± 17
ASA I or II (%)	74.4	78.1
Women (%)	58.7	60.6
Weight (kg)	74.5 ± 17.7	73.2 ± 14.5
Baseline ward systolic blood pressure (mm Hg)	122 ± 19	123 ± 20
Low ward heart rate (beats/min)	71 ± 10	68 ± 11
Cardiovascular disease (%)	52.6	60.6
History of respiratory disease (%)	11.3	11.0
Smokers (%)	26.3	21.2
History of hepatic disease (%)	8.2	5.1

N_2O, nitrous oxide.
Values are expressed as a percentage or as the average ± SD.

Table 3. Variables Associated With Anesthesia

	N_2O	No N_2O
Premedication		
Triazolam (%)	50	49
Morphine (%)	26	18
Thiopental (mg)	389 ± 183	428 ± 208
Fentanyl (μg)	228 ± 105	231 ± 127
Vecuronium (mg)	10.1 ± 4.4	10.1 ± 3.8
Maintenance end-tidal isoflurane (%)		
10–60 min	0.54 ± 0.28	0.70 ± 0.35[a]
>60 min	0.64 ± 0.32	0.85 ± 0.35[a]
Lowest intraoperative temperature (°C)	34.9 ± 0.8	35.0 ± 0.8
Duration of anesthesia (min)	178 ± 50	178 ± 54

N_2O, nitrous oxide.
Values are expressed as a percentage of patients with the indicated characteristic or as average ± SD.
[a] $P < 0.0001$.

Table 4. Hemodynamics During Anesthesia

	10–60 min		>60 min	
	N_2O^a	No N_2O^b	N_2O^a	No N_2O^b
Systolic blood pressure (mm Hg)				
Highest	141 ± 31	147 ± 37	147 ± 32	148 ± 33
Median	108 ± 19	114 ± 24	115 ± 22	117 ± 24
Lowest	87 ± 17	90 ± 16[c]	90 ± 17	91 ± 20
Heart rate (beats/min)				
Highest	82 ± 16	85 ± 20	87 ± 17	86 ± 16
Median	66 ± 12	68 ± 13	70 ± 14	71 ± 14
Lowest	59 ± 10	59 ± 11	59 ± 12	60 ± 13

N_2O, nitrous oxide.
Values are expressed as the average ± SD.
[a] $n = 133$.
[b] $n = 137$.
[c] $P = 0.05$ comparing N_2O and no-N_2O values.

ples, clearly was greater in the group given N_2O. That is, the fraction of isoflurane MAC was 0.2 (i.e., 20%) higher in patients anesthetized without N_2O, but the contribution of N_2O equaled 0.5–0.6 (50%–60%) of a MAC.

Values for intraoperative and postoperative (recovery room) blood pressure and heart rate did not differ between groups (Table 4 and 5), with one exception: patients given N_2O had a slightly lower systolic blood pressure (87 ± 17 vs 90 ± 16; mean ± SD) for the 10–60 min after the start of anesthesia. No trend suggested that intraoperative blood pressure might be higher in the patients given N_2O; all average blood pressures were numerically (if not statistically) *lower* if N_2O was used. Although intraoperative heart rate varied considerably within each group (note the standard deviation for rate in Table 4), the average rate was normal in both groups, with no suggestion that tachycardia was a frequent finding. Finally, the range of blood pressures and heart rates did not differ as a function of the presence or absence of N_2O.

The duration of anesthesia did not differ between anesthetic groups (Table 3). The time from the end of anesthesia to extubation did not differ between anesthetic groups, nor did the duration of stay in the recovery room. The duration of hospital stay did not differ between anesthetic groups. Comparing the values for these variables within each surgical subgroup revealed no significant differences (although times differed between subgroups).

Administration of N_2O did not contribute to postoperative analgesia, as reflected in the pain score (Table 6). Only patients recovering from total hip replacements received morphine postoperatively, with no difference in dose requirement between anesthetic groups. Orientation to place progressed equally rapidly in both groups (Table 6).

The incidence of remembered dreaming during anesthesia did not differ between anesthetic groups (Table 7). However, the incidence of remembered events during anesthesia (some frightening) approached significance in patients not given N_2O. The use of N_2O clearly did not predispose to dreaming or remembrance, and the percentage of patients who remembered or dreamed was less in the patients given N_2O. Nearly 99% of patients in both groups were satisfied with their anesthesia or had a few minor problems (Table 7). No difference was apparent between the two groups.

The results of the symptom questionnaire for the N_2O and no-N_2O groups were surprising because we found no significant differences and only two cases approaching significance, despite the 90 comparisons made (Table 1). Similarly, we found fewer differences than might have been expected by chance when we

Table 5. Hemodynamics During Recovery

	First hour		Second hour		>Second hour	
	N_2O[a]	No N_2O[b]	N_2O	No N_2O	N_2O	No N_2O
Systolic blood pressure (mm Hg)						
Highest	142 ± 26	143 ± 27	137 ± 21	139 ± 22	139 ± 25	138 ± 21
Median	130 ± 23	130 ± 24	129 ± 20	130 ± 20	129 ± 19	130 ± 20
Lowest	118 ± 21	118 ± 22	122 ± 20	122 ± 20	119 ± 20	121 ± 20
Heart rate (beats/min)						
Highest	90 ± 16	87 ± 15	82 ± 15	81 ± 15	84 ± 14	82 ± 15
Median	81 ± 14	79 ± 15	77 ± 14	75 ± 14	77 ± 14	76 ± 14
Lowest	74 ± 13	72 ± 14	72 ± 13	70 ± 14	72 ± 14	71 ± 14

N_2O, nitrous oxide.
Values are expressed as the average ± SD.
[a] $n = 133$.
[b] $n = 137$.

Table 6. Pain and Orientation Immediately After Anesthesia

	Time after admission to the recovery room							
	15 min		30 min		60 min		90 min	
	N_2O	No N_2O	N_2O	No N_2O	N_2O	No N_2O	N_2O	No N_2O
Pain score[a]								
0	20	27	8	10	2	3	1	2
1	43	42	34	40	22	34	14	23
2	20	23	26	31	33	34	41	45
3	10	7	23	16	37	20	36	23
4	7	1	9	3	6	9	8	7
Percent of patients oriented to place	57	59	77	81	91	91	95	96

N_2O, nitrous oxide.
[a] Given as the percentage of patients at each score.

Table 7. Awareness During Anesthesia, Satisfaction, and Duration of Hospitalization

	N_2O	No N_2O
Dreaming during anesthesia	7 (5.3)[a]	12 (8.8)
Remembering events during anesthesia	1 (0.8)	6 (4.5)[b]
Fear at recall of these events	0	4 (3.0)[c]
Complete satisfaction	102 (82)	104 (79)
A few minor problems	20 (16)	26 (20)
Some major problems	2 (1)	0
Complete dissatisfaction	0	2 (1)
Days of hospitalization	8.1 ± 5.0	7.8 ± 4.4

N_2O, nitrous oxide.
[a] Data are given as number of patients with percentage in parentheses.
[b] $P = 0.067$ as compared with the nitrous oxide group.
[c] $P = 0.053$ as compared with the nitrous oxide group.

made the same analysis within surgical groups using 270 comparisons. For patients having carotid endarterectomies, no significant ($P < 0.05$) differences were found. Of patients having total hip replacements, those given N_2O had less trouble concentrating (21% [10/48] vs 41% [20/49]; $P = 0.048$) on postoperative day 1 but not on other days. The N_2O group also was less sleepy during the day (77% [37/48] vs 92% [45/49]; $P = 0.053$). Among patients having transsphenoidal hypophysectomies, the N_2O group had a significantly higher incidence of vomiting (70% [33/47] vs 43% [22/51]; $P = 0.008$) and more frequently experienced nausea (68% [32/47] vs 51% [26/51]; $P = 0.102$) on the first postoperative day. However, these effects vanished by the end of the first day and did not reappear. The N_2O group in this subset of patients also tended to have a higher incidence of sore throat (70% [33/47] vs 49% [25/51]; $P = 0.041$) during the first day but not during subsequent days.

Table 1 provides the raw symptom data. These also were examined for changes from the preoperative values, but such comparisons yielded no additional insights. The average number of new symptoms in patients given N_2O was 5.4 ± 2.7 vs 5.3 ± 2.7 in patients not given N_2O. Patients undergoing total hip replacement with N_2O had marginally fewer new symptoms (4.7 ± 2.2 vs 5.6 ± 2.8; $P = 0.058$).

The incidence of peripheral neuropathy did not differ as a function of N_2O. Decreased scores were not more frequent in patients given N_2O. On postoperative day 1, the incidence of decreased scores for patients given N_2O was 29.7% ($n = 37$) vs 29.4% ($n = 34$) for those not given N_2O. On day 2, these values were 33.3% in both groups ($n = 36$ and 33, respectively), and on day 3, 16.0% ($n = 25$) and 18.2% ($n = 22$). Decreased scores were matched by increased scores so that, on average, the absolute scores did not decrease in either group. Orientation to time, place, and person was complete for nearly all patients in both groups (one exception on day 2 for each group) within 1 day after anesthesia. The results for the Glasgow Coma Score did not differ between groups.

Results of the preoperative digit-span test were the same for both anesthetic groups (11.2 ± 1.9 vs 11.2 ± 2.1 for N_2O versus no N_2O). Test scores decreased in both groups on the first (10.6 ± 2.2 and 10.6 ± 2.1) and second (10.8 ± 2.1 and 11.0 ± 2.3) postoperative days, but differences were not significant. By postoperative days 5–7, the test value for the N_2O group (11.1 ± 2.2) had returned to the preoperative level, but that for the group not given N_2O (12.1 ± 2.2) had increased significantly ($P < 0.05$). However, one should take into account that by days 5–7 only 39 patients given N_2O and 41 not given N_2O were available for testing, compared with almost all patients on day 2.

The incidence of untoward outcomes did not differ between the two anesthetic groups (Table 8). Hypoxemia was the most frequent outcome, followed by infections and reoperation.

Average preoperative temperature (measured orally) was identical in both anesthetic groups (36.7 ± 0.4°C). Intraoperative temperatures did not differ among anesthetic groups at any time (Table 3). Maximum postoperative temperatures also did not differ (37.9 ± 0.7°C, N_2O; and 37.8 ± 0.6°C, no N_2O). The highest (12,200 ± 3700 vs 11,400 ± 3400) and lowest (9900 ± 4100 vs 9200 ± 3500) white blood cell counts also did not differ between anesthetic groups.

No interaction between aging and possible untoward effects of N_2O was found. For example, aging did not increase hypoxemia associated with administration of N_2O.

Table 8. Outcomes

Item	N_2O n (%)	No N_2O n (%)
Hypoxemia		
Transsphenoidal hypophysectomy	0	1 (2.0)
Total hip arthroplasty	21 (42)	16 (32)
Carotid endarterectomy	7 (21)	4 (11)
Total	28 (21)	21 (15)
Atelectasis		
Total hip arthroplasty	2 (4.0)	3 (6.0)
Total	2 (1.5)	3 (2.2)
Pneumothorax		
Total	0	0
Pulmonary edema		
Carotid endarterectomy	0	1 (2.8)
Total	0	1 (0.7)
Pneumonia		
Total hip arthroplasty	0	1 (2.0)
Total	0	1 (0.7)
Suspected infection		
Transsphenoidal hypophysectomy	1 (2.0)	3 (5.9)
Total hip arthroplasty	6 (12)	2 (4.0)
Total	7 (5.3)	5 (3.6)
Bacteremia		
Total	0	0
Wound infection		
Transsphenoidal hypophysectomy	1 (2.0)	0
Total hip arthroplasty	2 (4.0)	0
Total	3 (2.3)	0
Urinary tract infection		
Total hip arthroplasty	1 (2.0)	3 (6.0)
Carotid endarterectomy	0	1 (2.8)
Total	1 (0.8)	4 (2.9)
Reoperation		
Transsphenoidal hypophysectomy	1 (2.0)	1 (2.0)
Total hip arthroplasty	1 (2.0)	2 (4.0)
Carotid endarterectomy	4 (12)	3 (8.3)
Total	6 (4.5)	6 (4.4)
Hepatic injury		
Total hip arthroplasty	3 (6.1)	2 (4.1)
Myocardial infarction		
Carotid endarterectomy	1 (7.1)	3 (19)
Death		
Carotid endarterectomy	1 (2.9)	0
Total	1 (0.8)	0
Any untoward outcome, including hypoxemia[a]		
Transsphenoidal hypophysectomy	3 (6.1)	5 (9.8)
Total hip arthroplasty	26 (52)	22 (44)
Carotid endarterectomy	9 (26)	11 (31)
Total	38 (29)	38 (28)
Any untoward outcome, excluding hypoxemia[a]		
Transsphenoidal hypophysectomy	3 (6.1)	4 (7.8)
Total hip arthroplasty	11 (22)	12 (24)
Carotid endarterectomy	4 (12)	8 (22)
Total	18 (14)	24 (18)

N_2O, nitrous oxide.

When neither group had positive findings for a given variable, no data are given (e.g., no patient having transsphenoidal hypophysectomies who were given or not given nitrous oxide had evidence of atelectasis). Data for hepatic injury and myocardial infarction are given only for patients having total hip arthroplasties and carotid endarterectomies (respectively) because those were the only groups examined for these variables.

[a] For the last two sets of tabulations, the first number is the number of patients who showed any outcome. Because a given patient may have had more than one outcome but would be counted only once, the total may be less than the sum of the preceding values. The number in parentheses is the percentage of the total available for that measurement.

Discussion

Despite theoretical, epidemiologic, and experimental evidence suggesting that N_2O might have various undesirable effects, we were unable to demonstrate such effects in this study or in parallel studies of pulmonary (16), myocardial (15), hepatic (17), or hematopoietic (18,19) function. The absence of harmful effects is particularly reassuring because we studied patients potentially vulnerable to injury from N_2O, including older patients (20), those undergoing significant surgical trauma (total hip arthroplasty), and those having significant circulatory disease (carotid endarterectomy).

Additionally, the data fail to suggest a trend that might have become significant in a larger population. Some of the data in Table 8 may suggest an exception; that is, the average incidence of suspected infection or wound infection was greater (but not significantly so) in patients given N_2O. However, in a parallel study of a small group ($n = 26$) of patients randomly assigned to anesthesia with and without N_2O for resection of acoustic neuromas, we found the incidence of suspected infection to be *greater* in those not given N_2O (7/13 vs 3/13 given N_2O) (21). As in the present study, this difference was not significant; moreover, combining the data for suspected infection from both studies yields no trend.

The preceding results support the continuing use of N_2O for the typical surgical patient. None of our results indicate that inactivation of methionine synthase injures such a patient. However, our findings do not exclude that inactivation by N_2O may adversely affect critically ill patients (10) or those deficient in vitamin B_{12} (22). Nor do they preclude that N_2O might increase the incidence of late-developing adverse outcomes. However, several of our patients remained hospitalized for 1–2 wk (especially those having hip operations), and no delayed outcomes were noted. Similarly, our findings do not rule out untoward effects of some of the known attributes of N_2O. The one death in our series was that of a patient who had a stroke after carotid endarterectomy under N_2O anesthesia. Were there air emboli enlarged by N_2O (23)? Results from other large, prospective, randomized studies also suggest that administration of N_2O does not increase mortality. For example, mortality was not different in 279 patients given N_2O plus narcotic compared with 259 patients given subarachnoid tetracaine or bupivicaine (5.9% compared with 6.6%, respectively) in elderly patients undergoing surgery for treatment of hip fracture (24).

We have suggested that the absence of even a trend indicating an untoward effect of N_2O indicates that N_2O produces no harm, or at least none greater than that produced by isoflurane alone. However, the absence of an untoward effect in a series of nearly 300 patients, only half of whom received the test agent (N_2O), does not rule out the possibility of an untoward effect. If one assumes that no untoward effect was found in 150 patients given N_2O, this only rules out ($P < 0.05$) the possibility of a long-run risk of an untoward effect exceeding a 2% rate (25). To reduce this possibility to 0.1% would require that we find no untoward effect in 3000 patients (i.e., 6000 total patients). Perhaps a future, larger, study will provide us with such statistics.

Several of the pharmacologic findings in the present study merit comment. As would be expected, the use of N_2O decreased the administered concentration of isoflurane (Table 3). However, the decrease was not as great as might be expected from the contribution of N_2O to MAC. That we observed no consistent difference between groups in blood pressure or heart rate (Table 4) suggests that the anesthetizing concentration of isoflurane chosen by each anesthesiologist was selected, in part, to maintain a "safe" circulatory state that did not compromise blood pressure. Our results in patients are thus consistent with those obtained in volunteers where a given MAC-multiple was associated with a higher blood pressure when N_2O was used with a potent agent (13,14). Although N_2O has an analgesic effect that might be predicted to attenuate the cardiovascular response to surgical stimulation, this quality neither lowered blood pressure or heart rate nor limited the range (i.e., the lability) in these variables (Table 4).

Despite the lower blood solubility of N_2O, patients given this agent did not awaken more rapidly (Table 6). This result may be attributed to the similar isoflurane concentrations used in both groups (Table 3).

Our patients given N_2O had a lower (not significant) incidence of dreaming or memory of events during anesthesia (Table 7). End-tidal isoflurane concentrations were probably not a factor because they were similar for patients who did and did not dream or remember. Similarly, end-tidal concentrations of isoflurane with and without N_2O did not differ between dreamers and nondreamers. However, the four patients who were frightened (none given N_2O) had lower dialed and end-tidal isoflurane concentrations for the 10–60-min and >60-min periods after the start of anesthesia. For example, the median dialed concentration for the 10–60-min period after the start of anesthesia was 0.62% ± 0.25% vs 1.14% ± 0.55% for the patients who were not frightened ($P < 0.02$), and end-tidal concentrations were 0.52% ± 0.29% vs 0.73% ± 0.34% ($P = 0.26$), respectively, After 60 min of anesthesia, the dialed concentrations were 0.75% ± 0.29% vs 1.19% ± 0.52% ($P < 0.05$), with respective end-tidal concentrations of 0.58% ± 0.28% vs 0.87%

± 0.34% ($P = 0.09$). The end-tidal values for the frightened patients are about 0.5 MAC, values approaching MAC-awake (26). Perhaps values of 0.75 MAC are needed to abolish fearful memories (or inadequate effect) of anesthesia.

Other reports advise that remembrance under anesthesia (evoked by suggestion of an action while under anesthesia) is independent of anesthetic concentration (27) and can occur at deep levels of anesthesia (28). However, examination of the methods in these reports suggests that another interpretation may be possible. In Bennett's study, most of the 11 patients who responded to hypnotic suggestion under anesthesia (27) were, in fact, lightly anesthetized. The exact level of anesthesia cannot be calculated because no end-tidal concentrations were measured nor were flow rates given. We have estimated (roughly) the likely highest end-tidal concentrations (assuming normal ventilation and no rebreathing), and for 10 of the 11 patients we have calculated a combined (N_2O plus potent inhaled agent) MAC of 0.75 ± 0.17. The 11th patient had a calculated combined MAC of 1.65. Similarly, Levinson (28) believed that the electroencephalographic tracings from his patients indicated a level of "very deep (ether) anaesthesia." In fact, the tracings showed slow frequency-high voltage activity that changed to lower voltage and higher frequency with stimulation, characteristics consistent with a light level of anesthesia. Clark and Rosner (29) found that visual or noxious stimuli caused changes in the electroencephalogram only at isoflurane concentrations lower than 40% of MAC. Similarly, high voltage-slow frequency electroencephalographic tracings occur at blood isoflurane concentrations equivalent to 0.4–1.1 MAC (30). Higher concentrations usually result in burst suppression. Further studies are needed to define the exact MAC levels preventing remembrance of frightening events; lacking such studies, it may be prudent to consider that 0.8–1 MAC may be needed.

Despite the increase in muscle tone produced by N_2O administration (31), the use of this agent was not associated with greater doses of vecuronium (Table 3). However, this finding may not be a fair indication of the need for relaxant because the surgical demand for relaxation was limited.

Although N_2O provides analgesia, we found no residual analgesia after anesthesia with this agent (Table 6). In fact, patients given N_2O had a greater incidence of higher pain scores (3 or 4) at each measurement, the difference reaching significance ($P < 0.05$) 30 min after anesthesia. However, the greater presence of pain did not increase blood pressure or heart rate (Table 5). Nitrous oxide is thought to exert its analgesic effect by a mechanism common to that of narcotics (32). Is the greater postoperative pain felt by patients given N_2O the result of a process that parallels tolerance to narcotics? An alternative explanation might be that the elimination of N_2O is more rapid than the elimination of isoflurane, and higher isoflurane concentrations were given to patients anesthetized without N_2O, which resulted in more prolonged analgesia. This explanation seems unlikely, because a more rapid rate of recovery is not evident in the time to orientation (Table 6).

We had anticipated that the responses to the 18 questions asked preoperatively and postoperatively might reveal several differences in symptoms between the anesthetic groups (Table 1). An increase in the incidence of coughing, sputum production, or sore throat might have been predicted from the expansion of the endotracheal tube cuff by N_2O with subsequent trauma to the larynx and trachea. No trend suggested such an effect except, perhaps, the greater incidence of sore throats among patients given N_2O for transsphenoidal hypophysectomies. Similarly, the expansion of internal gas spaces might have increased (but did not increase) the incidence of headache (sinusitis), stuffy nose (sinusitis), or earache.

Numbness and tingling is a nonspecific neurologic finding associated with occupational exposure to N_2O (9), but was not a finding in our study. We also found no objective evidence of neurologic injury associated with the use of N_2O. These findings suggest that exposure to N_2O for a single surgical procedure lasting 10 h does not produce neurologic injury. Such a result is not in conflict with previous studies demonstrating injury from use of N_2O, where injury was produced by longer (chronic) often repeated administration, i.e., abuse, of N_2O (7,8).

Our findings are similar to those of Scheinin et al. in that the use of N_2O decreased the concentration of isoflurane required to provide adequate anesthesia (4). Both Scheinin et al. and Guiffre and Gross (33) found that the use of N_2O increased intestinal distention in patients having abdominal surgery. Scheinin et al. further reported that N_2O was associated with a delay in return of bowel function and a prolongation of hospitalization, whereas neither we nor Guiffre and Gross found a delay or prolongation. In addition to the use of air in their control group, Scheinin et al. applied a "bowel washout" for 2 days before operation, their patients were given a liquid diet for the day before operation, and 200 mL of air was deliberately injected into the stomachs of their patients during surgery. Each of these factors may have increased the volume of intestinal air and thus enhanced the absolute expansion of volume produced by N_2O.

Whether N_2O causes vomiting is controversial (4,33–38). We found a greater incidence of vomiting in patients having transsphenoidal hypophysectomies soon (but not late) after anesthesia that included N_2O. If N_2O caused the greater incidence, the absence of this effect in our patients given N_2O might be related to the relative youth of those having transsphenoidal hypophysectomies; their average age was 39 ± 14 yr for those given N_2O and 42 ± 15 yr for those not given N_2O.

In summary, we found that the addition of N_2O to isoflurane for maintenance of anesthesia only subtly, if at all, altered the course of anesthesia and the development of untoward outcomes. The use of N_2O may have diminished the risk of remembrance and fear during anesthesia. In some patients, its use may have increased the incidence of vomiting and sore throat. Our findings do not indicate that the use of N_2O is dangerous in a typical patient having elective surgery.

We gratefully acknowledge the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny. Expert editorial assistance was provided by Winifred von Ehrenberg.

References

1. Saidman LJ, Hamilton WK. We should continue to use nitrous oxide. In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985:345–53.
2. Hornbein TF. Epilogue. In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985:355–7.
3. Eger EI II. Should we not continue to use nitrous oxide? In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985: 339–43.
4. Scheinin B, Lindgren L, Scheinin TM. Peroperative nitrous oxide delays bowel function after colonic surgery. Br J Anaesth 1990;64:154–8.
5. Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985.
6. Moseley H, Kumar AY, Shankar KB, Rao PS, Homi J. Should air-oxygen replace nitrous oxide-oxygen in general anaesthesia? Anaesthesia 1987;42:609–12.
7. Lassen HCA, Henriksen E, Neukirch F, Kristensen HS. Treatment of tetanus. Severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. Lancet 1956;i:527–30.
8. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 1978;ii:1227–30.
9. Cohen EN, Brown BW, Wu ML, et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980;101:21–31.
10. Amos RJ, Amess JAL, Hinds CJ, Mollin DL. Incidence and pathogenesis of acute megaloblastic bone-marrow change in patients receiving intensive care. Lancet 1982;ii:835–9.
11. Cahalan MK, Prakash O, Rulf ENR, et al. Addition of nitrous oxide to fentanyl anesthesia does not induce myocardial ischemia in patients with ischemic heart disease. Anesthesiology 1987;67:925–9.
12. Roizen MF, Plummer GO, Lichtor L. Nitrous oxide and dysrhythmias. Anesthesiology 1987;66:427–31.
13. Eisele JH Jr. Cardiovascular effects of nitrous oxide. In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985:125–56.
14. Dolan WM, Stevens WC, Eger EI II, et al. The cardiovascular and respiratory effects of isoflurane-nitrous oxide anaesthesia. Can Anaesth Soc J 1975;21:557–68.
15. Kozmary SV, Lampe GH, Benefiel D, et al. No finding of increased myocardial ischemia during or after carotid endarterectomy under anesthesia with nitrous oxide. Anesth Analg 1990;71:591–6.
16. Lampe GH, Wauk LZ, Whitendale P, et al. Postoperative hypoxemia after nonabdominal surgery: a frequent event not caused by nitrous oxide. Anesth Analg 1990;71:597–601.
17. Lampe GH, Wauk LZ, Whitendale P, Way WW, Murray W, Eger EI II. Nitrous oxide does not impair hepatic function in young or old surgical patients. Anesth Analg 1990;71:606–9.
18. Waldman FM, Koblin DD, Lampe GH, Wauk LZ, Eger EI II. Hematologic effects of nitrous oxide in surgical patients. Anesth Analg 1990;71:618–24.
19. Koblin DD, Tomerson BW, Waldman FM, Lampe GH, Wauk LZ, Eger EI II. Effect of nitrous oxide on folate and vitamin B_{12} metabolism in patients. Anesth Analg 1990;71:610–7.
20. Hoorn RJK, Filkweert JP, Westerink D. Vitamin B_{12}, B_2 and B_6 deficiency in geriatric patients, measured by coenzyme stimulation of enzyme activity. Clin Chim Acta 1975;61:151–64.
21. Lampe GH, Wauk LZ, Donegan JH, et al. Effect on outcome of prolonged exposure of patients to nitrous oxide. Anesth Analg 1990;71:586–90.
22. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12}-deficient subjects? JAMA 1986;255:1605–6.
23. Munson ES, Merrick HC. Effect of nitrous oxide on venous air embolism. Anesthesiology 1966;27:783–7.
24. Davis FM, Woolner DF, Frampton C, et al. Prospective, multicenter trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. Br J Anaesth 1987;59:1080–8.
25. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? JAMA 1983;249:1743–5.
26. Stoelting RK, Longnecker DE, Eger EI II. Minimal alveolar concentrations on awakening from methoxyflurane, halothane, ether and fluroxene in man: MAC awake. Anesthesiology 1970;33:5–9.
27. Bennett HL, Davis HS, Giannini JA. Non-verbal response to intraoperative conversation. Br J Anaesth 1985;57:174–9.
28. Levinson BW. States of awareness during general anaesthesia. Br J Anaesth 1965;37:544–6.
29. Clark DL, Rosner BS. Neurophysiologic effects of general anesthetics. I. The electroencephalogram and sensory evoked responses in man. Anesthesiology 1973;38:564–82.
30. Homi J, Konchigeri HN, Eckenhoff JE, Linde HW. A new anesthetic agent—Forane®: preliminary observations in man. Anesth Analg 1972;51:439–47.
31. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man. Anesth Analg 1982;61:553–6.
32. Finck AD. Nitrous oxide analgesia. In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985:41–55.
33. Guiffre M, Gross JB. The effects of nitrous oxide on postoperative bowel motility. Anesthesiology 1986;65:699–700.
34. Lonie DS, Harper NJN. Nitrous oxide anaesthesia and vomiting. Anaesthesia 1986;41:703–7.

35. Melnick BM, Johnson LS. Effects of eliminating nitrous oxide in outpatient anesthesia. Anesthesiology 1987;67:982–4.
36. Muir JJ, Warner MA, Offord KP, Buck CF, Harper JV, Kunkel SE. Role of nitrous oxide and other factors in postoperative nausea and vomiting: a randomized and blinded prospective study. Anesthesiology 1987;66:513–8.
37. Korttila K, Hovorka J, Erkola O. Nitrous oxide does not increase the incidence of nausea and vomiting after isoflurane anesthesia. Anesth Analg 1987;66:761–5.
38. Sengupta P, Plantevin OM. Nitrous oxide and day-case laparoscopy: effects on nausea, vomiting and return to normal activity. Br J Anaesth 1988;60:570–3.

Effect on Outcome of Prolonged Exposure of Patients to Nitrous Oxide

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Prolonged (several days or repeated) exposure to nitrous oxide (N_2O) can cause injury or death. To assess whether relatively prolonged anesthesia with N_2O in normal patients might similarly cause untoward effects, we investigated whether the addition of N_2O to isoflurane anesthesia caused injury to patients having surgical resection of acoustic neuroma lasting approximately 10 h. Twenty-six patients undergoing surgical resection of acoustic neuroma were randomly assigned to a regimen that included or excluded N_2O (50%–60%) during isoflurane anesthesia plus intravenous adjuvants. On average, slightly less isoflurane (0.24%) was used during anesthesia with N_2O. We measured standard clinical variables (blood pressure, heart rate), oxygen saturation, neurologic status, pain, and the incidence and type of morbid outcomes. Exposure to N_2O did not increase the incidence of morbid outcomes (including hepatic injury, infection, or hypoxemia), prolong hospitalization, or increase common postoperative complaints such as nausea, vomiting, coughing, or headache. Patients anesthetized with either regimen were equally satisfied with their anesthetic.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHESIA, DURATION—nitrous oxide; outcome.

Prolonged exposure to nitrous oxide (N_2O) may cause aplastic anemia and death (1). The proposed mechanism of such toxicity is inactivation of methionine synthase, an enzyme important to the synthesis of DNA, and methionine, an essential amino acid. In humans, exposure to 50%–70% N_2O for 3 h decreases hepatic methionine synthase activity by 75% (2,3). However, we have been unable to demonstrate that short-term (2–4 h) exposure to N_2O increases untoward clinical outcomes or decreases patient satisfaction with the anesthetic experience (4). We undertook the present study to assess whether a longer period of exposure (approximately 10 h) might increase the incidence of untoward events postoperatively. Such an exposure substantially exceeds that imposed on all but a few patients. If N_2O causes untoward effects in normal patients, we anticipated that this prolonged exposure would reveal such effects.

Materials and Methods

Twenty-six patients presenting for elective resection of acoustic neuroma consented to participate in our institutionally approved study. Premedication (triazolam, and/or morphine, or none) and intraoperative fentanyl and edrophonium/atropine were administered at the discretion of the anesthesiologist. All patients received isoflurane, thiopental, and vecuronium, but were randomly assigned to an anesthetic regimen including either 50%–60% N_2O/30%–40% oxygen (O_2) (n = 13) or 100% O_2 (n = 13). After intubation, a heat-and-moisture exchanger (Humid-vent) was placed at the outside end of the endotracheal tube in all patients. Inhaled isoflurane concentrations were adjusted to maintain clinically acceptable levels of anesthesia as determined by the attending anesthesiologist. Ventilation was controlled, and total gas flows of 5 L/min were maintained throughout surgery. Tidal volume was 10–15

Supported in part by PO1 AG03104A, the Anesthesia Research Foundation, and a grant from Anaquest, Inc.

Received from the Departments of Anesthesia and Neurosurgery, University of California, San Francisco, California. Accepted for publication June 27, 1990.

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mL/kg, and the respiratory rate was adjusted to maintain PA_{CO_2} at approximately 30–35 mm Hg. Pulse rate and systolic blood pressure values were measured at least every 5 min intraoperatively (using a Dynamap recorder) to determine their median, lowest, and highest values. Esophageal (operating) or axillary (recovery room) temperatures were recorded throughout anesthesia and the recovery period. We recorded the duration of anesthesia and hospitalization. The methods used to gather data were identical to those described more extensively in a companion paper (4).

Using a recording pulse oximeter (Ohmeda Biox II, Ohmeda Instruments, Inc.), we measured oxygen saturation continuously for 24 h after initiation of anesthesia and made single determinations of saturation on postoperative days 2, 3, and 5, 6, or 7. The patients breathed room air postoperatively. We defined hypoxemia as a saturation of less than 86%, and recorded its duration during the first 24 postoperative hours.

For the first 7 days after anesthesia, we recorded the highest oral temperature occurring in each 8-h period throughout the day and night. We recorded hematocrit and white blood cell counts when these data were ordered by surgeons, including the highest and lowest postoperative white blood cell counts and sampling times.

We assessed the development of untoward perioperative clinical events including hypoxemia (see above); atelectasis (radiographic evidence); pneumothorax (radiographic evidence); pulmonary edema (radiographic evidence); pneumonia (radiographic evidence and increased white blood cell count plus fever); suspected infection (oral temperature >38°C throughout two consecutive 8-h periods with an associated white blood count >13,000); bacteremia (positive blood culture); wound infection (as defined by the surgeon); urinary tract infection (by culture); reoperation; and death. Blood samples were drawn immediately before surgery and on postoperative days 1 and 3 to obtain blood for testing hepatic function (alanine aminotransferase [ALT], also known as SGPT; alkaline phosphatase; bilirubin).

In the recovery room, we obtained a "pain score" at 15, 30, 60, and 90 min after admission to the recovery room: 0 = patient is unresponsive; 1 = patient reports no pain; 2 = little pain; 3 = a lot of pain; and 4 = unbearable pain. Simultaneously, we assessed the patient's orientation to place. At 90 min, we asked whether the patient remembered dreaming during anesthesia, or remembered events during anesthesia, or was frightened by such events. We recorded the time from the end of anesthesia to the first administration of narcotic (usually codeine, sometimes morphine), total dose of narcotic, and length of stay in the recovery room.

We assessed neurologic status preoperatively and on postoperative days 1, 2, and 5, 6, or 7 using (a) the Glasgow Coma Score; (b) a 40-point scoring of peripheral neuropathy (motor, pinprick, temperature, and proprioception in hands and feet); (c) orientation to time, place, and person; and (d) the digit-span test (forward and backward).

Patients were asked a series of 20 questions (symptom checklist) preoperatively and on postoperative days 1, 2, and 5, 6, or 7 to determine the incidence of coughing, headache, nausea, vomiting, numbness or tingling, confusion, and earache. On postoperative day 2 we also asked patients to rate their satisfaction with the anesthetic.

All data collection (including patient interviews) and analyses were performed by individuals unaware of the patient's anesthetic regimen. We calculated mean values and change and percent change from preoperative values, and we made comparisons using Student's *t*-test, analysis of variance, Fisher's exact test, or χ^2 analysis. We accepted a value of $P < 0.05$ as representing statistical significance.

Table 1. Patient Demographic and Clinical Characteristics

	N_2O	No N_2O
n	13	13
Age (yr)	49.7 ± 10.8	47.6 ± 10.2
Sex (male)	10	8
Weight (kg)	78.8 ± 13.9	79.6 ± 15.8
Smoking history	2	3
ASA I or II	12	11
ASA III	1	2
Cardiovascular disease	1	4
Respiratory disease	0	1
Hepatic disease	2	0
Alcohol abuse	0	0

N_2O, nitrous oxide.
All values are expressed as the number or as mean ± SD.

Results

The two study groups did not differ demographically or clinically (Table 1). Aspects of anesthetic management that were similar in each group included drugs used for premedication, doses of fentanyl, thiopental, and vecuronium, duration of anesthesia, median heart rate, and median and low systolic blood pressure during surgery (first 10 min, 10–60 min, 60 min to end) (Table 2). Nitrous oxide did not affect the lability of blood pressure and pulse rate (i.e., the

Table 2. Variables Associated With Anesthesia

	N_2O	No N_2O
Premedication		
Triazolam (*n*)	2	0
Morphine (*n*)	1	0
Thiopental (mg)	500 ± 220	470 ± 170
Fentanyl (μg)	1000 ± 520	1450 ± 910
Vecuronium (mg)	13.5 ± 5.3	14.3 ± 5.1
Maintenance end-tidal isoflurane (%)		
10–60 min	0.53 ± 0.29	0.58 ± 0.24
>60 min	0.85 ± 0.15	1.09 ± 0.28[a]
Duration of anesthesia (h)	9.3 ± 2.4	9.9 ± 3.8
Median heart rate (beats/min)		
First 10 min	88 ± 13	88 ± 11
10–60 min	86 ± 12	83 ± 13
>60 min	88 ± 13	85 ± 15
Median systolic blood pressure (mm Hg)		
First 10 min	117 ± 14	124 ± 18
10–60 min	110 ± 13	112 ± 14
>60 min	110 ± 11	114 ± 12
Lowest systolic blood pressure		
First 10 min	96 ± 16	105 ± 19
10–60 min	98 ± 16	104 ± 14
>60 min	93 ± 8	94 ± 10
Number with intraoperative O_2 saturation <86%	0	1
Lowest operating room saturation	94.6 ± 2.8	93.8 ± 5.6

N_2O, nitrous oxide; O_2, oxygen.
Values are expressed as number of patients, percentage, or mean ± SD.
[a] $P = 0.013$.

Table 3. Adverse Outcomes

Outcome	N_2O	No N_2O
Any adverse outcome, excluding hypoxemia	4 (31)	7 (54)
Any adverse outcome, including hypoxemia	4 (31)	8 (62)
Hypoxemia	1 (8)	5 (38)
Pneumonia	1 (8)	1 (8)
Suspected infection	3 (23)	7 (54)

N_2O, nitrous oxide.
Values are expressed as the number of patients; percentages are given in parentheses.

Table 4. Perioperative Hepatic Function

	N_2O	No N_2O
ALT (IU)		
Preoperative	20 ± 7	26 ± 12
Postoperative day 1	23 ± 8	25 ± 10
Postoperative day 3	24 ± 10	26 ± 12
Maximum change	6.8 ± 10.7	2.2 ± 8.3
Bilirubin (mg/dL)		
Preoperative	0.58 ± 0.29	0.51 ± 0.14
Postoperative day 1	0.80 ± 0.24	0.68 ± 0.25
Postoperative day 3	0.78 ± 0.24	0.55 ± 0.12[a]
Maximum change	0.30 ± 0.20	0.18 ± 0.18
Alkaline phosphatase (IU)		
Preoperative	87 ± 103	67 ± 23
Postoperative day 1	76 ± 94	60 ± 21
Postoperative day 3	84 ± 83	66 ± 30
Maximum change	−2.2 ± 18.4	2.7 ± 20.5

ALT, alanine aminotransferase; N_2O, nitrous oxide.
Values are expressed as mean ± SD.
[a] $P = 0.01$.

difference between low and high values). Median blood pressure in the recovery room did not differ between groups. Similarly, the lowest temperatures in the operating and recovery rooms, and the total intraoperative blood loss, were nearly identical for the two groups. Patients anesthetized with N_2O required less isoflurane to maintain anesthesia (Table 2), but the difference was less than anticipated based on the MAC contribution provided by 50%–60% N_2O. The intraoperative and postoperative incidence of O_2 saturation <86% did not differ between groups (Tables 2 and 3). There was no trend suggesting that the incidence would have been higher in patients given N_2O had a greater number of patients been studied.

The absolute and percent changes in ALT, bilirubin, and alkaline phosphatase from preoperative to maximal postoperative values also did not differ significantly between groups (Table 4). Baseline values were normal in all patients. In the group given N_2O, ALT increased slightly (3.1 ± 6.6 IU vs −1.6 ± 4.9 IU in the O_2 group; $P = 0.05$) on the first, but not the third, postoperative day. Bilirubin levels were significantly higher on the third postoperative day, but this change was not clinically significant. No jaundice was observed, and the highest bilirubin value in the group given N_2O was 1.3 mg/dL.

Nitrous oxide did not increase the incidence of any adverse outcome (Table 3). In addition, no patient in either group had evidence of atelectasis, pneumothorax, pulmonary edema, bacteremia, wound infection, or urinary tract infection. No patient died, and none required reoperation. Most of the adverse outcomes occurred in the first 2 days after surgery.

The analgesic effects of N_2O did not linger into the postoperative period, as indicated by the pain scores (Table 5). The doses of narcotic given postoperatively did not differ between the two anesthetic groups. Orientation to place, time, and person tended to progress more slowly (but not significantly so) in the group given only O_2 (Table 5).

Postoperative symptoms or change from preoperative symptoms (as defined by responses to the 20 questions in the symptom checklist) did not differ between anesthetic groups. Nitrous oxide did not increase the incidence of nausea or vomiting (9/13 in

Table 5. Recovery From Anesthesia

	Time after admission to the recovery room							
	15 min		30 min		60 min		90 min	
	N_2O	O_2	N_2O	O_2	N_2O	O_2	N_2O	O_2
Pain score[a]								
0	77	85	62	69	38	54	8	31
1	0	15	8	23	8	15	15	23
2	15	0	15	8	31	15	46	23
3	8	0	8	0	8	8	8	23
4	0	0	8	0	15	8	23	0
Percent of patients oriented to place	23	8	23	23	62	31	77	38[b]

N_2O, nitrous oxide; O_2, oxygen.

[a] Percentage of patients having a given pain score at the indicated times: 0 = unresponsive; 1 = no pain; 2 = little pain; 3 = a lot of pain; and 4 = unbearable pain.

[b] $P = 0.111$ by Fisher's exact test (two-tailed).

each group). Almost all patients developed a new headache, regardless of choice of anesthetic. Four patients in each group developed new numbness or tingling on one or more postoperative days. Fewer patients given N_2O (four) felt faint or dizzy than did patients given O_2 (eight), but this difference was not statistically significant. Six patients in each group had trouble concentrating postoperatively. Three patients in each group developed a new earache (not attributable to surgery), and nine in each group developed a stuffy nose. Overall, 9.2 ± 2.6 new symptoms per patient were reported in the group given N_2O, and 9.7 ± 3.2 new symptoms per patient in the group given O_2. Satisfaction with the choice of anesthetic did not differ: 11 patients in each group were completely satisfied or had only minor complaints.

No patient had any memory of events during anesthesia. Two patients given O_2, but none given N_2O, remembered dreaming during anesthesia. None were frightened by the dreaming. During the first 10–60 and >60 min of anesthesia, these two patients had median end-tidal concentrations of isoflurane of 0.6% and 1.1%, values not dissimilar to concentrations given their peers who received N_2O (see Table 2).

Alkaline phosphatase levels were normal throughout (Table 4). White blood cell counts increased in both groups, but there was no difference between groups (highest value for the group given N_2O was 17,500 ± 5000 vs 18,800 ± 7600 for the group given O_2 only). This finding may have been influenced by administration of corticosteroids (given to all patients). Similarly, no difference was found for the lowest white blood cell count. The maximum postoperative temperature was similar in both groups (38.2 ± 0.4°C with N_2O and 38.4 ± 0.4°C with O_2).

The results for the Glasgow Coma Score did not differ between groups on any day, the average scores being identical (and entirely normal) for the groups on days 1 and 5–7, and differing (decreased by one point) for only one patient (O_2 group) on day 2. Peripheral neuropathy scores (decreases indicating the development of neuropathy) decreased in the group given no N_2O, only O_2. The score had decreased by 0.41 ± 0.79 on postoperative days 5–7 in the group given O_2, but had increased by 0.20 ± 0.42 in the group given N_2O plus O_2 ($P = 0.04$). Nitrous oxide did not impair orientation to place, time, and person except for a decrease in score by one point for one patient in each group on the first postoperative day. Digit-span recall did not differ between groups preoperatively (12.0 ± 2.9 vs 11.0 ± 1.6, N_2O vs O_2), on postoperative day 1 (10.3 ± 1.6 vs 9.3 ± 2.4), day 2 (10.8 ± 1.8 vs 9.6 ± 2.2), or days 5–7 (11.2 ± 1.5 vs 10.0 ± 2.9). Nitrous oxide did not prolong hospitalization. Patients receiving N_2O stayed 7.0 ± 2.2 days, and those given only O_2 8.6 ± 3.2 days ($P = 0.15$).

Discussion

Our results do not confirm the hypothesis that prolonged N_2O administration might be injurious to surgical patients or increase the incidence of undesirable symptoms such as nausea or vomiting. Clearly, chronic administration of N_2O can injure the brain, peripheral nerves, and bone marrow. However, our data from this and a previous study (4) indicate that a 2–10-h exposure causes no such injuries (16 h was the longest exposure to N_2O in the present study). We found no evidence of an increased incidence of injury to lung, liver, brain, or peripheral nerves. Suggestions of changes attributable to N_2O included only a slight increase in serum levels of bilirubin. The group given only O_2 had a slightly (but not statistically significantly) *greater* incidence of peripheral neuropathy, hypoxemia, and suspected infection. The absence of even a trend indicating an adverse outcome associated with N_2O suggests that a larger data base would not provide different findings. Data acquired by us for operations of 2–4-h duration support this conclusion (4–9), but have less authority than the present study, which imposed a threefold greater exposure to N_2O. Only rarely will a patient breathe N_2O for a longer period than the patients described in the present report.

Our data do not indicate the limit of safe exposure to N_2O in normal patients. Such a limit must exist, but may be measured in days rather than hours. A shorter exposure might adversely affect particular patients, such as those with preexisting deficiencies in vitamin B_{12} or folate (10), but we have not studied these patients.

Lampert (11) suggested that N_2O inactivation of methionine synthase might account for the multiple nerve palsies reported after prolonged administration of N_2O to a diabetic patient (12). The authors of the original study disputed this possibility (13). One of our patients was diabetic and was given N_2O. We found no adverse effect in this patient, but cannot extrapolate from our study population to predict the risk of prolonged N_2O exposures in a diabetically compromised patient.

The discovery that prolonged exposure to N_2O inactivates methionine synthase and can thereby impair DNA synthesis has established a concern about the routine use of N_2O in anesthesia for elective surgery. Our results and those from companion studies indicate that these concerns may be unwarranted. It appears that N_2O may be administered to normal patients for up to 10 h without toxic effects.

We gratefully acknowledge the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny. Expert editorial assistance was provided by Winifred von Ehrenberg.

References

1. Lassen HCA, Henriksen E, Neukirch F, Kristensen HS. Treatment of tetanus. Severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. Lancet 1956;i:527–30.
2. Koblin DD, Waskell L, Watson JE, Stokstad ELR, Eger EI II. Nitrous oxide inactivates methionine synthetase in human liver. Anesth Analg 1982;61:75–8.
3. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. Anesthesiology 1988;68:213–6.
4. Eger EI II, Lampe GH, Wauk, LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85.
5. Waldman FM, Koblin DD, Lampe GH, Wauk LZ, Eger EI II. Hematologic effects of nitrous oxide in surgical patients. Anesth Analg 1990;71:618–24.
6. Kozmary SV, Lampe GH, Benefiel D, et al. No finding of increased myocardial ischemia during or after carotid endarterectomy under anesthesia with nitrous oxide. Anesth Analg 1990;71:591–6.
7. Lampe GH, Wauk LZ, Whitendale P, et al. Postoperative hypoxemia after nonabdominal surgery: a frequent event not caused by nitrous oxide. Anesth Analg 1990;71:597–601.
8. Lampe GH, Wauk LZ, Whitendale P, Way WW, Murray W, Eger EI II. Nitrous oxide does not impair hepatic function in young or old surgical patients. Anesth Analg 1990;71:606–9.
9. Lampe GH, Donegan JH, Rupp SM, et al. Nitrous oxide and epinephrine-induced arrhythmias. Anesth Analg 1990;71:602–5.
10. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12}-deficient subjects? JAMA 1986;255:1605–6.
11. Lampert BA. Multiple nerve palsies after anesthesia—a complication of nitrous oxide use? Anesth Analg 1989;69:136–7.
12. Navalgund AA, Jahr JS, Gieraerts R, Chang J-L, Garla PGN. Multiple nerve palsies after anesthesia and surgery. Anesth Analg 1988;67:1002–4.
13. Navalgund AA, Jahr JS, Gieraerts R, Change J-L, Price GS, Garla PGN. Multiple nerve palsies after anesthesia and surgery—a complication of nitrous oxide use? Anesth Analg 1989;69:137.

No Finding of Increased Myocardial Ischemia During or After Carotid Endarterectomy Under Anesthesia With Nitrous Oxide

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Nitrous oxide (N_2O) has been implicated as a cause of myocardial ischemia. We investigated whether substitution of N_2O for a portion of the anesthesia supplied by isoflurane increased myocardial ischemia in patients at risk for such ischemia. Seventy patients having carotid endarterectomies (63 patients) or other carotid surgery (seven patients) were prospectively, randomly assigned to an anesthetic regimen that included or excluded N_2O. All other aspects of anesthetic management were similar, except for greater concentrations of oxygen and isoflurane in patients not given N_2O. Perioperative monitoring for myocardial ischemia and infarction included 12- or 5-lead electrocardiography, transesophageal echocardiography, and creatine kinase isoenzyme levels. By transesophageal echocardiographic or electrocardiographic criteria, 44% of patients given oxygen but only 21% of those given N_2O had myocardial ischemia intraoperatively ($P = 0.065$). Similarly, myocardial infarction, identified by changes in creatine kinase isoenzymes, occurred in only one patient given N_2O but in three given oxygen (not significantly different). Thus we found no trend indicating a greater incidence of myocardial ischemia or infarction associated with the use of N_2O.

Key Words: ANESTHETICS, GASES—nitrous oxide. HEART, MYOCARDIAL ISCHEMIA, MYOCARDIAL INFARCTION—nitrous oxide.

Because of its perceived safety, nitrous oxide (N_2O) is widely used in patients who have myocardial ischemia. However, several reports implicate N_2O as a cause of such ischemia. In dogs with an imposed critical stenosis of the coronary artery, N_2O increases postsystolic shortening of the myocardium (1,2), a change that can be interpreted as an early indicator of myocardial ischemia. Nitrous oxide also increases postsystolic shortening in the isolated perfused dog heart (3), depresses the rate of recovery of the "stunned" canine myocardium, and increases the risk of death from coronary artery occlusion in dogs (4). It causes epicardial coronary artery vasoconstriction in both dogs (5,6) and pigs (7).

Only one clinical study of N_2O indicates that patients may manifest metabolic and electrocardiographic (ECG) evidence of myocardial ischemia (8). However, these findings were not statistically significant, and the changes observed may have resulted from changes in hemodynamics (e.g., hypotension), rather than being a direct effect of N_2O. Accordingly, we investigated whether the use of 60% N_2O with isoflurane and fentanyl increases the incidence of myocardial ischemia above that associated with isoflurane and fentanyl alone. We chose to study the ischemic effects of N_2O in patients undergoing carotid endarterectomy (or operations on the carotid artery) because such patients have a high incidence of coronary artery disease, which makes them susceptible to perioperative ischemia and infarction. The incidence of ischemic heart disease may be 40% in asymptomatic patients and 92% in patients with symptoms or abnormal ECGs indicative of myocardial ischemia (9–11). Additionally, carotid endarterectomy may be associated with labile hemodynamics that may predispose surgical patients to ischemia by altering myocardial work, myocardial perfusion pres-

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Supported in part by P01 AG03104A, the Anesthesia Research Foundation, and a grant from Anaquest, Inc.

Received from the Departments of Anesthesia and Cardiology, University of California, San Francisco, California. Accepted for publication August 6, 1990.

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sure, and heart rate (time available for myocardial perfusion).

Methods

Seventy patients scheduled for carotid endarterectomy or other surgery on the carotid artery consented to participate in our institutionally approved study. Sixty-three had a carotid endarterectomy. Seven had other procedures: carotid-carotid bypass (one patient); carotid aneurysm repair (two patients); and carotid dilatation (four patients). All patients received isoflurane, fentanyl (2–5 μg/kg), thiopental (2–5 mg/kg), and vecuronium, but were randomly assigned to receive 60% N_2O/40% oxygen (O_2) ($n = 34$) or 100% O_2 ($n = 36$). Four patients who had contralateral carotid endarterectomies separated by at least 6 wk were studied twice. The anesthetic for the first procedure was assigned randomly, and the alternate regimen was used for the second procedure. Premedication (triazolam, morphine, or none) and inhaled concentrations of isoflurane were determined by the attending anesthesiologist, and not by study protocol. Neuromuscular blockade was antagonized with edrophonium and atropine before extubation. All patients were mechanically ventilated with tidal volumes of 10 mL/kg at a rate sufficient to produce an end-tidal carbon dioxide (CO_2) of 30–35 mm Hg.

Previously prescribed cardiac and antihypertensive medications were given the morning of surgery. Routine perioperative monitoring for all patients included a 5-lead ECG and pulse oximeter, precordial or esophageal stethoscope, temperature sensor (esophageal), nerve stimulator, and mass spectrometer measurements. Insertion of a radial arterial catheter permitted transduction of blood pressure and acquisition of blood for blood/gas analyses.

We monitored for myocardial ischemia using 12-lead ECG (Marquette MAC 1, Marquette Electronics, Milwaukee, Wis.) and transesophageal echocardiography (TEE). A baseline 12-lead ECG was obtained before anesthetic induction. After induction and intubation, a 9-mm gastroscope having a 3.5- or 5.0-mHz ultrasound transducer (Diasonics, Milpitas, Calif., or Hewlett-Packard, Palo Alto, Calif.) connected to an ultrasonograph (Diasonics or Hewlett-Packard) was inserted through the mouth into the esophagus or stomach to produce a cross-sectional, short-axis view of the left ventricle at the midpapillary level. Images obtained were recorded on half-inch VHS videotape.

Measurements were made preinduction (except for TEE or anesthetic variables), 3 min after intubation (postinduction), 3 min before carotid cross-clamping (preclamp), 3 min after carotid cross-clamping (postclamp), 3 min after removal of the carotid cross-clamp (postunclamp), and during skin closure. We also obtained ECG and TEE recordings when systolic blood pressure or heart rate changed 30% from the baseline (ward) value for 3 or more minutes. We considered such changes indicative of a "hemodynamic event."

Twelve-lead ECGs were obtained on postoperative days 1, 2, and 3 and compared with the preoperative recording. Data from patients who had intraventricular conduction block or paced rhythm were excluded from this analysis. We also measured creatine kinase enzyme (CKs) and isoenzyme (MB fraction) levels preoperatively and on postoperative days 1 and 2 in approximately the last half of our patients ($n = 34$; 18 given N_2O, 16 not given N_2O). Finally, we interviewed patients preoperatively and on postoperative days 1, 2, and 5 and asked if they had "chest pain or angina." Patients were unaware of the anesthetic group to which they were assigned. The attending anesthesiologist was not blinded to the patient's study group, had access to the 5- and 12-lead ECG and TEE data, but did not discuss the interpretation of these data with the research staff.

Experts unaware of the choice of anesthetic analyzed the data. Transesophageal echocardiographic data were analyzed for new segmental wall motion abnormalities, as described previously (12). Two observers read the short-axis views of the left ventricle. The ventricle was divided into four quadrants, and the wall for each quadrant was graded as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic. Myocardial ischemia was diagnosed if wall motion worsened by more than one grade without concurrent worsening of all walls. A third, senior echocardiographer (M.K.C.) arbitrated any grading discrepancy between the two observers. The 12-lead ECG data were read by two observers for changes in baseline of the ST segment 80 ms after the J point. Ischemia was defined as elevation or depression of the ST segment by 1 mm or more.

Perioperative myocardial infarction was diagnosed by the development of Q waves on the ECG or by the finding of a total CK > 100 IU with >4% MB isoenzyme present.

Data for the groups were compared using unpaired Student's *t*-test for parametric data and Fisher's exact test (two-tailed) for counted data. We accepted $P \leq 0.05$ as significant.

Table 1. Patient Demographic and Clinical (Preoperative) Characteristics

	N_2O	No N_2O
n	34	36
Age (yr)	65 ±10	67 ± 8
ASA I or II (%)	26	33
Women (%)	41	56
Weight (kg)	74 ± 13	72 ± 14
Baseline ward systolic blood pressure (mm Hg)	140 ± 20	140 ± 21
Low ward pulse rate (beats/min)	68 ± 10	67 ± 12
Hypertensive (%)	56	56
History of myocardial infarct <1 yr (%)	0	6
History of myocardial infarct >1 yr (%)	18	19
No current angina (%)	85	94
Medications		
Antihypertensives (%)	9	17
β-Blockers (%)	15	19
Calcium channel blockers (%)	12	14
Nitrates (%)	9	11
Diuretics (%)	26	39
History of respiratory disease (%)	21	19
Smokers (%)	24	31

N_2O, nitrous oxide.

Values for age, weight, baseline ward systolic blood pressure, and low ward pulse rate are expressed as an average ± SD.

Table 2. Variables Associated With Anesthesia

	N_2O	No N_2O
n	34	36
Premedication		
Triazolam (%)	24	17
Morphine (%)	6	0
Thiopental (mg)	290 ± 170	350 ± 200
Fentanyl (μg)	180 ± 180	150 ± 100
Vecuronium (mg)	13 ± 6	12 ± 5
Maintenance end-tidal isoflurane (%)		
10–60 min	0.53 ± 0.20	0.74 ± 0.27[a]
>60 min	0.60 ± 0.23	0.83 ± 0.28[a]
Lowest intraoperative temperature (°C)	35.6 ± 0.6	35.7 ± 0.6
Duration of anesthesia (min)	196 ± 54	189 ± 51

N_2O, nitrous oxide.

Values are expressed as a percentage of the patients with the indicated characteristic or as an average ± SD.

[a] $P < 0.001$, compared with the N_2O group.

Results

The two study groups were not significantly different demographically or clinically (Table 1), but some trends were suggested. Patients not given N_2O on average were more likely to receive calcium channel blocking, diuretic, nitrate, and antihypertensive drugs preoperatively, suggesting that they may have had more severe cardiovascular disease. However, these differences were not statistically significant.

Most aspects of anesthetic management were similar for the two groups, including the use of adjuvant agents for premedication and of thiopental, fentanyl, and vecuronium (Table 2). A higher concentration of isoflurane was given to the patients who did not receive N_2O. Esophageal temperature and the duration of anesthesia did not differ between the two groups.

The intraoperative use of cardiovascular drugs also did not differ between groups: 75% of patients given N_2O and 73.5% given O_2 received phenylephrine; 25% versus 12.5% received β-blockers; 3.1% versus 5.9% received nitroglycerin; and 3.1% versus 5.9% required atropine beyond the dose given with edrophonium.

The incidence of hemodynamic events (30% change from ward median systolic blood pressure or heart rate for at least 3 min) did not differ between groups either in sum or for individual hemodynamic events (Table 3). Twenty-one patients given N_2O (61.8%) had at least one hemodynamic event, as did 21 patients (58.3%) given O_2. Similarly, hemodynamic events per patient equaled 1.44 ± 1.60 in the N_2O group and 1.78 ± 1.35 in the O_2 group. The large standard deviations indicate the wide variation in the number of hemodynamic events per patient and the skewed nature of these results. The median value for each anesthetic group was one hemodynamic event per patient. Of 110 (total) hemodynamic events 44 were hypertension, 29 tachycardia, 10 both hypertension and tachycardia, 19 hypotension, and 8 bradycardia.

Nine of 61 patients (2 of 28 given N_2O; 7 of 33 given O_2) had ECG evidence of intraoperative ischemia (no significant difference). Evidence for ischemia was found primarily in leads V_2, V_4, and V_5. Intraoperative 12-lead ECG data from nine patients were not evaluated for ischemia because of intraventricular conduction defect (five patients), paced rhythm (two patients), immediate reoperation (one patient), or lost data (one patient).

The TEEs showed evidence of intraoperative ischemia in 16 of 62 patients (eight patients with unreadable echocardiograms). Two of the patients having echocardiographic evidence of ischemia also had ECG evidence of ischemia. Of the 1804 TEE short-axis quadrant views, 195 were unreadable (10.8%). In the N_2O group, 5 of 29 patients (17.2%) had at least one intraoperative ischemic episode, compared with 11 of 33 patients (33.3%) in the O_2 group (not a statistically

Table 3. Numbers of Patients Having Specific Hemodynamic Events[a]

	N_2O			O_2		
Event	*n*	Median number of events per patient	Number ischemic	*n*	Median number of events per patient	Number ischemic
Hypertension	12	1	3	9	2	3
Hypotension	5	1	2	6	2	4
Tachycardia	7	1	2	11	1	6
Bradycardia	0	—	—	3	2	1
Hypertension and tachycardia	2	3	1	3	1	1
No event	13	—	1	15	—	6[b]

For each anesthetic group, *n* is the total number of patients having a specific hemodynamic event. This is followed by the median number of events; the average is not given because of the skewed nature of the data. The third column for each anesthetic group is the number of patients who had ischemia by either electrocardiographic or transesophageal echocardiographic criteria and had the indicated hemodynamic event. Because a patient might have more than one event, the total numbers for all events exceed the total number of patients in the study. Similarly, ischemic events listed with a given event may not be associated with that event and may be counted more than once.

[a] Defined as a change >30% from the ward value and lasting >3 min.

[b] $P = 0.12$ compared with N_2O group, by Fisher's two-tailed exact test.

significant difference). No pattern was apparent during the time at which ischemia occurred. Hemodynamic events usually were not associated with ischemia as defined by TEE or ECG (Table 3). Transesophageal echocardiographic changes indicative of intraoperative ischemia usually occurred in patients (10 of 16, or 62.5%) who experienced a hemodynamic event, but this did not differ from the incidence of hemodynamic events in patients who had no TEE evidence of ischemia (32 of 54, or 59.3%).

Postoperative CK isoenzyme levels in 4 of 34 patients indicated postoperative myocardial infarction. Three of the four were in the oxygen group. Two of the four patients also had postoperative ECG evidence of ischemia (ST elevation or depression); the remaining two patients had bundle branch blocks (one preexisting and one new) that precluded evaluation of ischemia. Two additional patients who had positive CK isoenzymes preoperatively had negative isoenzymes postoperatively. No patient ever displayed Q waves on the ECG.

Five patients (three given N_2O) had postoperative ECG evidence of ischemia. Two additional patients (O_2 only) had new left bundle branch blocks. No patient responded affirmatively when asked (as all were) if they had "chest pain or angina" on postoperative days 1, 2, and 5.

Discussion

We did not find that N_2O causes myocardial ischemia or infarction in patients with coronary artery disease. However, our power to find a significant change was limited by the small size of our population. Of patients in whom intraoperative ischemia could be assessed from the ECG, 15% (9/61) had evidence of ischemia. Given the average size of each group, N_2O would have had to increase this to 45% (a 30% increase) to give a power of 0.8 in a one-tailed test for detection of a significant difference ($P < 0.05$) (13). Indeed, we did see a 15% difference between groups (2/28 for the group given N_2O compared with 7/33 for the group not given N_2O), but the change favored finding ischemia with the group *not* given N_2O. Similarly, of patients in whom intraoperative ischemia could be assessed from TEE, 26% (16/62) had evidence of ischemia. Nitrous oxide would have had to have increased this to 58% (a 32% increase) to give a power of 0.8. We found a 16% difference (5/29 compared with 11/33), but again the change favored finding ischemia with the group *not* given N_2O. Finally, evidence of myocardial infarction (defined by CK changes) were found in 12% of patients (4/34). This would have to be increased to 52% (a 40% increase) to have a power of 0.8. We found a 13% difference (1/18 compared with 3/16), but again the change favored finding ischemia with the group *not* given N_2O. In summary, we found a trend suggesting that the use of N_2O was associated with *less* intraoperative ischemia and a *lower* incidence of myocardial infarction but emphasize that these trends were not statistically significant and that we did not have the power to detect small differences between the effects of the two anesthetic regimens.

In designing this study, we debated whether to use O_2 or O_2 plus N_2 as the background gas for the patients not receiving N_2O. We selected O_2 because that is the usual choice of the clinician who decides not to apply N_2O. That is, we considered that the use of O_2 increased the clinical relevance of our results. The substitution of N_2O for some of the O_2 and isoflurane might have affected our results by altering hemodynamics. This would be the implication of results from studies in volunteers where substitution of N_2O produced a greater arterial blood pressure, peripheral resistance, and cardiac output/oxygen consumption at a given MAC level (14,15). However, under the conditions of our study, the measurements we made of pulse rate and blood pressure did not show any meaningful difference between the patients who did and did not receive N_2O (16). In part, this may have resulted from the imposition of surgical stimulation. In part, it may have resulted from the application of a slightly higher MAC level (but lower concentration of isoflurane) in the patients given N_2O. In any event, we have no evidence indicating that alterations in hemodynamics affected our results.

Our results are consistent with those of two other studies in which patients undergoing coronary artery bypass graft surgery were anesthetized with fentanyl and given N_2O or nitrogen in a crossover design (17,18). The presence of myocardial ischemia was evaluated by both 12-lead ECG and TEE and did not occur more frequently in association with N_2O. Our study strengthens the conclusions from these previous studies in that our patients did not have the confounding effect of an operation upon the heart, and we studied patients throughout the operative experience.

The conclusion that N_2O does not adversely affect the patient with coronary artery disease is supported by results from studies in animals. In animal models in which critical stenosis of a coronary artery has been imposed but hemodynamics held constant, N_2O does not affect myocardial fiber shortening more than nitrogen (19), nor does it alter the duration of postsystolic shortening (20). These results probably differ from those from earlier studies suggesting an adverse effect of N_2O (3) because the design of the earlier studies did not maintain sufficient stability of hemodynamics.

Our results indicate that including N_2O in anesthesia for carotid artery surgery results in no more myocardial ischemia than replacing the N_2O with O_2 and isoflurane. This suggests that N_2O does not cause myocardial ischemia, but another possibility may exist. The use of N_2O decreased the requirement for isoflurane, which also has been implicated as causing ischemia (21). Possibly, both agents cause ischemia and do so to the same extent. If so, substitution of one for the other might not change the incidence of ischemia. However, because recent epidemiologic evidence does not implicate isoflurane as more likely than other inhaled anesthetics or narcotics to cause myocardial ischemia (22,23), this explanation is unlikely. The evidence presently available does not indicate that N_2O puts patients with coronary artery disease at greater risk of myocardial ischemia or infarction than other general anesthetics.

The editorial assistance of Winifred von Ehrenberg is gratefully acknowledged, as is the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny.

References

1. Philbin DM, Föex P, Drummond G, Lowenstein E, Ryder WA, Jones LA. Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology 1985;62:166–74.
2. Leone BJ, Philbin DM, Lehot JJ, Föex P, Ryder WA. Gradual or abrupt nitrous oxide administration in a canine model of critical coronary stenosis induces regional myocardial dysfunction that is worsened by halothane. Anesth Analg 1988;67:814–22.
3. Nathan HJ. Nitrous oxide worsens myocardial ischemia in isoflurane-anesthetized dogs. Anesthesiology 1988;68:407–15.
4. Siker D, Pelc LR, Kampine JP, Schmeling WT, Warltier DC. Nitrous oxide depresses functional recovery of stunned myocardium in dogs. Anesthesiology 1989;71:A476.
5. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. Anesthesiology 1987;66:273–9.
6. Wilkowski DA, Sill CJ, Bonta W, Owen R, Bove AA. Nitrous oxide constricts epicardial coronary arteries without effect on coronary arterioles. Anesthesiology 1987;66:659–65.
7. Pettis MS, Witzeling TM, Sill JC, Hughes JM, Rorie DK, Blaise GA. Nitrous oxide constricts coronary arteries in pigs via an endothelium dependent mechanism. Anesthesiology 1989;71: A533.
8. Reiz S. Nitrous oxide augments the systemic and coronary haemodynamic effects of isoflurane in patients with ischaemic heart disease. Acta Anaesthesiol Scand 1983;27:464–9.
9. Rokey R, Rolak LA, Harati Y, Kutka N, Verani MS. Coronary artery disease in patients with cerebrovascular disease: a prospective study. Ann Neurol 1984;16:50–3.
10. Tomatis LA, Fierens EE, Vergrugge GP. Evaluation of surgical risk in peripheral vascular disease by coronary arteriography: a series of 100 cases. Surgery 1972;71:429–35.
11. Hertzer NR, Beven EG, Young YR, et al. Coronary artery disease in peripheral vascular patients. Ann Surg 1984;199: 223–33.
12. Smith JS, Cahalan MK, Benefiel DJ, et al. Intraoperative detection of myocardial ischemia in high-risk patients: electrocardiography versus two-dimensional echocardiography. Circulation 1985;72:1015–21.
13. Hulley SB, Cummings SR. Designing clinical research. Baltimore: Williams & Wilkins, 1988:216–7.
14. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 1971;35:8–16.
15. Dolan WM, Stevens WC, Eger EI II, et al. The cardiovascular and respiratory effects of isoflurane-nitrous oxide anaesthesia. Can Anaesth Soc J 1974;21:557–68.

16. Eger EI II, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85.
17. Mitchell MM, Prakash O, Rulf ENR, et al. Nitrous oxide does not induce myocardial ischemia in patients with ischemic heart disease and poor ventricular function. Anesthesiology 1989;71: 526–34.
18. Slavik JR, LaMantia KR, Kopriva CJ, Prokop E, Ezekowitz MD, Barash PG. Does nitrous oxide cause regional wall motion abnormalities in patients with coronary artery disease? Anesth Analg 1988;67:695–700.
19. Cason BA, Mazer CD, Demas KA, Hickey RF. Nitrous oxide does not worsen ischemic left ventricular dysfunction in the pig. Anesthesiology 1988;67:A46.
20. Nathan HJ. Should nitrous oxide be used for patients with ischemic heart disease? Evidence of safety from a laboratory investigation. Anesthesiology 1988;69:A82.
21. Reiz S, Balfors E, Sorensen MB, Ariola S Jr, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59: 91–7.
22. Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989;70:179–88.
23. Tuman KJ, McCarthy RJ, Spiess BD, DaValle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 1989;70:189–98.

Postoperative Hypoxemia After Nonabdominal Surgery: A Frequent Event Not Caused by Nitrous Oxide

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LAMPE GH, WAUK LZ, WHITENDALE P, WAY WL, KOZMARY SV, DONEGAN JH, EGER EI II. Postoperative hypoxemia after nonabdominal surgery: a frequent event not caused by nitrous oxide. Anesth Analg 1990;71:597–601.

We tested whether anesthesia that includes nitrous oxide (N_2O) results in the development of intraoperative and postoperative pulmonary complications, including hypoxemia. We also tested whether aging contributes to the development of such complications, particularly when anesthesia includes N_2O. We randomly allocated patients having total hip replacements, carotid endarterectomies, or transsphenoidal hypophysectomies (total $n = 270$) to an anesthetic regimen with and without N_2O (stratified within surgical group). A heat-and-moisture exchanger was included in the anesthetic circuit of all patients. Patients were monitored perioperatively and for 1 wk after surgery using intermittent and continuous pulse oximetry to determine oxyhemoglobin saturation. Intraoperatively, mean oxygen (O_2) saturations were lower in patients given N_2O, particularly older patients. Hypoxemia (O_2 saturation <86%) developed in five patients receiving N_2O and in one receiving O_2. This difference was not significant. Administration of N_2O did not decrease postoperative O_2 saturation, nor did it alter the incidence of postoperative hypoxemia, cough, or sputum production.

Key Words: ANESTHETICS, GASES—nitrous oxide. OXYGEN, HYPOXEMIA—postoperative.

Whether anesthesia that includes nitrous oxide (N_2O) impairs perioperative pulmonary oxygenation appears to be controversial. An untoward effect of N_2O is consistent with the rapid absorption of this gas from alveoli with obstructed airways (1,2). Gawley and Dundee found an association between administration of N_2O and impaired *postoperative* oxygenation (3). Although Webb and Nunn found no association (4), they did not study the effects of N_2O in a prospective, randomized fashion, and examined only its intraoperative effects relative to nitrogen (N_2).

We designed the current study to define the role of N_2O in the development of intraoperative and postoperative pulmonary dysfunction. Because such dysfunction increases with age (5), we also examined whether aging alone, or in combination with N_2O, influenced the development of postoperative pulmonary dysfunction. A finding of an interaction would be consistent with the observations of Kitamura et al. (6), who found marked age-related changes in postoperative oxygenation in patients given N_2O.

Methods

Two hundred seventy patients scheduled for elective total hip arthroplasty ($n = 100$), carotid endarterectomy ($n = 70$), or transsphenoidal hypophysectomy ($n = 100$) consented to participate in our institutionally approved study. Preoperatively, we evaluated each patient for a history of respiratory disease, current medications, smoking, and complaints of cough or sputum. Patients were interviewed on the first postoperative day to collect new complaints of cough or sputum production. All patients received isoflurane, thiopental, and vecuronium, but were randomly assigned to receive 60% N_2O/40% oxygen (O_2) ($n = 133$) or 100% O_2 ($n = 137$). Blocks of 10 patients within each surgical group were randomized to receive or not receive N_2O. The randomization also was selected to assure an equal distribution within each block between patients given and not given N_2O. The intraoperative use of fentanyl and edro-

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Supported in part by PO1 AG03104A, the Anesthesia Research Foundation, and a grant from Anaquest, Inc.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication August 3, 1990.

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phonium/atropine was controlled by the attending anesthesiologist, not by study protocol. In all patients, after tracheal intubation, a heat-and-moisture exchanger (Humid-vent) was placed between the endotracheal tube and the anesthetic circuit. Ventilation was controlled, and total gas flows of 5 L/min were maintained throughout surgery. Tidal volume was 10–15 mL/kg, and the respiratory rate was adjusted to maintain P_{ACO_2} at approximately 30–35 mm Hg. Further details are supplied in our report describing the clinical pharmacology of N_2O (7).

Patients were monitored using pulse oximetry (Ohmeda Biox IV) preoperatively, at 60 and 120 min postoperatively, and on postoperative days 1, 2, 3, and 5. Measurements were taken during the sixth minute after the patient had breathed room air for 5 min. The lowest O_2 saturation value obtained during the sixth minute was recorded.

Of the 270 patients, the 141 having a carotid endarterectomy or total hip replacement (70 with N_2O and 71 with O_2) also were monitored using continuous pulse oximetry (Ohmeda Biox II) for a 24-h period beginning just before induction of anesthesia. Monitoring included hard-copy printout of heart rate and O_2 saturation. Values recorded in the 141 patients included the incidence and duration of postoperative oxyhemoglobin saturations <90% and <86%, the lowest O_2 saturation value, and the duration (number of consecutive minutes) of <86% saturation. Use of supplemental O_2 administration was determined by physicians and nurses not involved in the study, and such treatments were recorded. We also obtained samples of arterial blood 1 and 2 h after completion of surgery for measurement of Pa_{CO_2}, Po_2, and pH ($n = 148$).

All data collection, analysis, and patient interviews were performed by medical personnel blinded to the anesthetic regimen. The results from the two anesthetic groups were analyzed using *t*-tests, Fisher's exact test (two-tailed), and χ^2 analyses. Regression analyses were applied to define the effect of age and any interaction of aging and N_2O on postoperative pulmonary function. We considered changes to be statistically significant at a value of $P < 0.05$.

Table 1. Demographic and Clinical Characteristics

	N_2O	No N_2O
Age (yr)	54 ± 18	54 ± 17
ASA I or II (%)	74.4	78.1
Women (%)	58.7	60.6
Weight (kg)	74.5 ± 17.7	73.2 ± 14.5
Smoker (%)	26.3	21.2
Pack-year history[a]	20.6 ± 29.9	16.5 ± 25.3
Cough (%)	27	23
Sputum (%)	17	15
History of respiratory disease (%)	11.3	11.0
Bronchodilator therapy (%)	4.5	2.9
Oxyhemoglobin saturation before:		
Carotid endarterectomy (%)	95 ± 2	96 ± 2
Hip arthroplasty (%)	96 ± 2	96 ± 2
Transsphenoidal hypophysectomy (%)	96 ± 2	96 ± 2
All patients (%)	96 ± 2	96 ± 2

N_2O, nitrous oxide.
Values are expressed as a percentage or as mean ± SD.
[a] This includes all patients, even those who did not smoke at any time.

Table 2. Variables Associated With Anesthesia and Postoperative Care

	N_2O	No N_2O
Premedication		
Triazolam (%)	49.6	48.9
Morphine (%)	26.3	17.5
Fentanyl (μg)	228 ± 154	231 ± 127
End-tidal isoflurane 10–60 min (%)	0.54 ± 0.28	0.70 ± 0.35[a]
End-tidal isoflurane >60 min (%)	0.64 ± 0.33	0.85 ± 0.35[a]
Duration of anesthesia (min)	178 ± 50	178 ± 54
Intraoperative bronchospasm (%)	1.5	0
Morphine (mg) during first postoperative 24 h (hip patients only)	37 ± 15	35 ± 15
New postoperative cough (%)	31	38
New postoperative sputum production (%)	34	36

N_2O, nitrous oxide.
[a] $P < 0.0001$ compared with the N_2O group.

Results

The two study groups did not differ demographically or clinically (Table 1). Anesthetic management (Table 2) differed only in the administration of more isoflurane to patients not given N_2O. Oxyhemoglobin desaturation occurred during the course of surgery in one patient in each group; the patient given N_2O required discontinuation of its use. Hypoxemia (O_2 saturation <86%) occurred intraoperatively in five patients given N_2O and in only one receiving O_2 (Table 3). All hypoxemic episodes were transient (<2 min); four (all in the group given N_2O) occurred upon discontinuation of anesthesia after tracheal extubation.

Patients anesthetized with N_2O for hip replacement or carotid endarterectomy reached lower intraoperative O_2 saturations (93.3% ± 2.8%; $n = 73$) than those given O_2 (96.0% ± 5.2%; $n = 73$) ($P = 0.002$). The decrease in intraoperative saturation was great-

Table 3. Patients With Hypoxemia Within the First 24 h After Anesthesia

	N_2O	No N_2O
Patients with O_2 saturation <90% intraoperatively (%)[a]		
Carotid[b]	18.5	0
Hip[c]	9.3	4.5
Total	12.8	2.8
Patients with O_2 saturation <90% postoperatively (%)		
Carotid[b]	48.1	44.4
Hip[c]	72.0	77.3
Total	62.8	64.7
Patients with O_2 saturation <86% intraoperatively (%)		
Carotid[b]	7.4	0
Hip[c]	7.0	2.3
Total	7.1	1.4
Patients with O_2 saturation <86% postoperatively (%)		
Carotid[b]	14.8	7.4
Hip[c]	27.9	27.2
Total	22.8	19.7
Consecutive minutes per patient of intraoperative O_2 saturation <86%[a]		
Carotid[b]	0.07 ± 0.27	0
Hip[c]	0.09 ± 0.37	0.02 ± 0.15
Total	0.09 ± 0.33	0.01 ± 0.12
Consecutive minutes per patient of O_2 saturation <86%, in the recovery room		
Carotid[b]	0.19 ± 0.48	0.04 ± 0.19
Hip[c]	0.17 ± 0.39	0.12 ± 0.63
Total	0.14 ± 0.42	0.09 ± 0.50
Consecutive minutes of O_2 saturation <86%, after leaving recovery room		
Carotid[b]	0	0
Hip[c]	4 ± 17	5 ± 20
Total	3 ± 14	4 ± 17
Low intraoperative O_2 saturation (%)[a]		
Carotid	92 ± 7	96 ± 2[d]
Hip	94 ± 4	96 ± 3[e]
Total	93 ± 5	96 ± 3[f]
Low O_2 saturation (%) in recovery room		
Carotid	89 ± 1	90 ± 3
Hip	90 ± 4	90 ± 3
Total	90 ± 4	90 ± 3
Low O_2 saturation (%) after leaving recovery room		
Carotid	90 ± 2	91 ± 3
Hip	88 ± 4	86 ± 7
Total	88 ± 4	88 ± 7
Patients given O_2 after leaving recovery room (%)		
Carotid	100	94.7
Hip	23.3	18.2
Total	45.0	41.3

N_2O, nitrous oxide; O_2, oxygen.
Values are expressed as percentage or as mean ± SD.
[a] Including 10 min after extubation.
[b] For these determinations, continuous pulse oximetry was used; the *n* values are 27 patients given N_2O and 27 not given N_2O.
[c] Similarly, for these determinations the values are for 43 patients given N_2O and 44 not given N_2O.
[d] $P = 0.0019$ compared with the N_2O group.
[e] $P = 0.059$ compared with the N_2O group.
[f] $P = 0.0002$ compared with the N_2O group.

est in patients undergoing carotid endarterectomy with N_2O: 91.9% ± 6.7% ($n = 27$) vs 96.4% ± 1.7% ($n = 29$) in the O_2 group ($P = 0.002$).

Exposure to N_2O did not increase the immediate (recovery room) or later postoperative risk of hypoxemia. The percent decline in postoperative O_2 saturation over the six measurement intervals was slight (average decline <2% in the recovery room and <1% by postoperative day 3) and did not differ between groups (Table 4). There was no difference in the incidence of desaturation to 90% or 86% in the two anesthetic groups on postoperative days 2, 3, and 5–7. Blood gas values (pH, Pa_{CO_2}, P_{O_2}) for the first and second postoperative hours did not differ be-

Table 4. Postoperative Decline in Oxygen (O_2) Saturation

Group	Time after anesthesia					
	1 h	2 h	1 day	2 days	3 days	5 days
N_2O						
O_2 saturation (%)	−1.5 ± 3	−1.3 ± 3	−1.2 ± 3	−0.7 ± 3	−1.0 ± 2	−0.6 ± 2.0
n	116	123	125	126	132	38
O_2						
O_2 saturation (%)	−1.6 ± 2	−1.4 ± 3	−1.1 ± 2	−0.4 ± 2	−0.4 ± 2	−0.4 ± 2
n	120	129	134	127	125	41

N_2O, nitrous oxide.
Values for change in O_2 saturation are expressed as mean ± SD.

tween the groups anesthetized with ($n = 71$) and without ($n = 77$) N_2O for hip replacement or carotid endarterectomy.

Episodes of hypoxemia (O_2 saturation <90% or <86%) detected by continuous pulse oximetry were frequent in both groups, with no difference between groups (Table 3). Consecutive minutes of <86% saturation or the lowest saturation level also did not differ.

The incidence of supplemental use of O_2 was similar in patients who did and did not receive N_2O. Administration of O_2 during the first night after surgery markedly decreased the incidence of hypoxemia in patients recovering from hip replacement or carotid endarterectomy (0% compared with 29% in those who did not receive additional O_2: $P < 0.001$). In all patients, O_2 administration was transiently discontinued to assess the impact of breathing room air on saturation and on blood gas tensions.

Only two patients developed bronchospasm; this event occurred during anesthesia. Both patients were anesthetized with N_2O. New postoperative complaints of cough or sputum production occurred in 31% and 34%, respectively, of patients given N_2O and 38% and 36% of those given O_2. None of the differences between groups was significant.

Regression analysis revealed that older patients had lower postoperative O_2 saturation values ($F = 4.73$; $P < 0.05$). However, aging did not significantly increase the incidence of hypoxemia (O_2 saturation <86%), although a trend existed for such a correlation. No age-related effect of N_2O was found. A history of smoking was not associated with an increase in the incidence of postoperative hypoxemia (13.0% for smokers; 11.3% for nonsmokers). The fraction of patients who smoked in the N_2O group versus that in the O_2 group did not differ, and the pack-years of smoking for those who smoked did not differ (37.1 ± 31.8 vs 30.9 ± 27.5 pack-years, respectively). The use of N_2O did not affect the relationship of smoking and hypoxemia at any point of observation.

Discussion

Our findings show that N_2O (with isoflurane) produces no greater postoperative pulmonary dysfunction than anesthesia with isoflurane and O_2. They conflict with those of Gawley and Dundee (3), who found that anesthesia including N_2O impaired postoperative oxygenation. However, Gawley and Dundee humidified inspired gases only for study patients who did not receive N_2O. It is likely that humidification of inspired gases decreases the incidence of postoperative respiratory complications, the interpretation originally proposed by Gawley and Dundee. In our study, the incidence of postoperative respiratory complications (cough and/or sputum production; see Table 2) was higher than that reported by Gawley and Dundee (cough, 15%; sputum, 20%) when delivering humidified gases. This difference may be related to the method of humidification: we used a Humid-vent in all patients; they added water vapor to the inspired gases.

In designing this study, we debated whether to use O_2 or O_2 plus N_2 as the background gas for the patients not receiving N_2O. We selected O_2 because that is the usual choice of the clinician who decides not to apply N_2O. That is, we considered that the use of O_2 increased the clinical relevance of our results. However, this choice may have confounded our results by introducing an element of O_2 toxicity into the control group, thereby obscuring a subtle noxious pulmonary effect of N_2O (i.e., both groups may have experienced the same amount of injury but from different causes).

If we can ignore the concern expressed in the previous paragraph, we believe our study had the power to reveal an appreciable increase in detrimental outcomes associated with the use of N_2O or O_2. For example, were the true incidence of coughing or sputum 20%, we would have had a power of 0.8 to reveal an increase to 35% with our sample size of 135 per group (one-tailed test) (8). Similarly, we would have had a power of 0.8 to detect an increase from a mythical baseline of 50% to the 65% incidence of hypoxemia seen with N_2O.

Many of our results confirm previous findings of others (e.g., see the review by Marshall and Wyche) (9). It is not surprising that a lower O_2 saturation or hypoxemia occurred during and immediately after anesthesia with N_2O. The lower inspired concentration of O_2 administered to patients given N_2O obviously increases the potential for hypoxemia. The appearance of hypoxemia immediately after anesthesia with N_2O may be partially explained by diffusion hypoxia (10,11). These findings emphasize the importance of the use of supplemental O_2 during the immediate recovery period, particularly when N_2O has been used.

Independent of anesthetic technique, the incidence of episodic hypoxemia was significant during the first 24 h after carotid endarterectomy and total hip arthroplasty. Supplementation of inspired air with O_2 prevented hypoxemia. If the observed hypoxemia represents a risk, our finding has implications for postoperative management. Should not all similar patients receive supplemental O_2 the first night after surgery?

Similar to others, we found that postoperative O_2 saturation decreases with increasing age. Thus, postoperative administration of supplemental O_2 may be particularly important in the aged patient. The inverse relationship between O_2 saturation and increasing age was not affected by administration of N_2O.

Although other studies (12,13) have shown an association between a history of smoking and postoperative hypoxemia, we found none. We have no explanation for this difference in our patient population.

We may summarize our results as follows. The use of N_2O is associated with a decrease in oxyhemoglobin saturation intraoperatively that, in most patients, is too small to be of clinical importance. Postoperative hypoxemia occurs frequently in the absence of supplemental O_2, particularly in the older patient. However, postoperative hypoxemia is not related to the intraoperative administration of N_2O except, perhaps, for the diffusion hypoxia that may present immediately after anesthesia. Similarly, postoperative cough and sputum production are not increased by the intraoperative use of N_2O.

We gratefully acknowledge the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny, and the cooperation of residents and faculty at the University of California at San Francisco. Expert editorial assistance was provided by Winifred von Ehrenberg.

References

1. Eger EI II. Respiratory effects of nitrous oxide. In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985:109–23.
2. Dantzker DR, Wagner PD, West JB. Instability of lung units with low VA/Q ratios during O_2 breathing. J Appl Physiol 1975;38:886–95.
3. Gawley TH, Dundee JW. Attempts to reduce respiratory complications following upper abdominal operations. Br J Anaesth 1981;53:1073–8.
4. Webb SJS, Nunn JF. A comparison between the effect of nitrous oxide and nitrogen on arterial PO_2. Anaesthesia 1967; 22:69–80.
5. Wahba WM. Influence of aging on lung function—clinical significance of changes from age twenty. Anesth Analg 1983; 62:764–6.
6. Kitamura H, Sawa T, Ikezono E. Postoperative hypoxemia: the contribution of age to the maldistribution of ventilation. Anesthesiology 1972;36:244–52.
7. Eger EI II, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85.
8. Hulley SB, Cummings SR. Designing clinical research. Baltimore: Williams & Wilkins, 1988:216–7.
9. Marshall BE, Wyche MQ Jr. Hypoxemia during and after anesthesia. Anesthesiology 1972;37:178–209.
10. Sheffer L, Steffenson JL, Birch AA. Nitrous-oxide-induced diffusion hypoxia in patients breathing spontaneously. Anesthesiology 1972;37:436–9.
11. Rackow H, Salanitre E, Frumin MH. Dilution of alveolar gases during nitrous oxide excretion in man. J Appl Physiol 1961;16: 723–8.
12. Morton HJV. Tobacco smoking and pulmonary complications after operation. Lancet 1944;i:368–70.
13. Laszlo G, Archer GG, Darrell JH. The diagnosis of pulmonary complications of surgical operations. Br J Surg 1973;60:129–34.

Nitrous Oxide and Epinephrine-Induced Arrhythmias

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We asked whether the sympathomimetic effect of nitrous oxide (N_2O) predisposed patients receiving N_2O to arrhythmias in response to epinephrine administration. We also asked whether aging contributed to the development of arrhythmias, with or without N_2O. One hundred patients having transsphenoidal hypophysectomy were randomly assigned to receive anesthesia including ($n = 49$) or excluding ($n = 51$) N_2O. All patients were given an injection of epinephrine 1:200,000, with 0.5% lidocaine to produce hemostasis. Using intermittent 12-lead and continuous lead II electrocardiography, we determined the incidence of premature ventricular contraction, isorhythmic atrioventricular (AV) dissociation, and changes in T-wave morphology. Patients given N_2O had a significantly higher incidence of isorhythmic AV dissociation (61.2% vs 41.2%). A trend toward a higher incidence of multiple premature ventricular contractions (16.3% vs 7.8%) was not statistically significant. Both anesthetic groups had a high incidence of postoperative changes in T-wave morphology (46.9% in the N_2O group vs 50.9% in the group not given N_2O). Aging alone did not affect the incidence of ventricular ectopic beats, isorhythmic AV dissociation, or changes in electrocardiographic morphology, but correlated with the development of ventricular ectopy during N_2O anesthesia. We conclude that the use of N_2O correlated with a higher incidence of isorhythmic AV dissociation in response to injection of epinephrine with lidocaine.

Key Words: ANESTHETICS, GASES—nitrous oxide. HEART, ARRHYTHMIAS—ventricular, isorhythmic atrioventricular dissociation.

Nitrous oxide (N_2O) activates the sympathetic nervous system, causing an increase in plasma catecholamine levels (1). Results of an unpublished report indicate that N_2O sensitizes the myocardium in dogs to the ventricular-arrhythmic effects of epinephrine (2). Data from a recent study suggest that N_2O may cause isorhythmic dissociation or atrioventricular (AV) junctional rhythms (3). Both reports imply that N_2O might augment epinephrine's effects on ventricular or dissociative rhythms. Accordingly, we measured the intraoperative and postoperative incidence of both arrhythmias and changes in electrocardiographic (ECG) morphology in patients given epinephrine during transsphenoidal hypophysectomy under anesthesia with and without N_2O. Because the incidence of heart disease increases with aging (4), and because basal levels of catecholamines increase with aging (5) whereas reaction to catecholamines decreases (6), we also examined the effect of age on the incidence of ventricular and dissociative arrhythmias.

Methods

One hundred ASA I–III patients scheduled for elective transsphenoidal hypophysectomy for pituitary adenomas gave written consent to participate in our institutionally approved study. Preoperatively, we evaluated each for a history of cardiovascular disease and β-sympathetic blocking medication. We obtained a 12-lead ECG. The study protocol limited anesthetic premedications to triazolam, morphine, or no premedication. The protocol limited intraoperative medications to fentanyl and edrophonium/atropine plus isoflurane, thiopental, vecuronium, and N_2O. The

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Supported in part by PO1 AG03104A, the Anesthesia Research Foundation, and a grant from Anaquest, Inc.

Received from the Departments of Anesthesia and Neurosurgery, University of California, San Francisco, California. Accepted for publication August 2, 1990.

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doses of these drugs were controlled by the attending anesthesiologist, not by the study protocol. All patients received isoflurane, thiopental, and vecuronium, but were randomly assigned to receive 60% N_2O in oxygen (O_2) (49 patients) or O_2 alone (51 patients). Inhaled isoflurane concentrations were adjusted to maintain a level of anesthesia acceptable to the attending anesthesiologist. End-tidal isoflurane concentrations were measured by mass spectroscopy, and we recorded the median end-tidal values for the first hour of anesthesia and for the remainder of anesthetic administration. Ventilation was controlled to produce a mild hypocapnia. Arterial blood pressure values were obtained with an automated (Dynamap) device every minute during the 15-min period after injection of epinephrine.

Epinephrine, 1:200,000, in 0.5% lidocaine was injected by the surgeon. Lead II of the ECG was continuously recorded from 15 s before injection until 15 min after. We recorded the total dose of epinephrine administered. In the recovery room we recorded a 12-lead ECG.

All ECGs were interpreted by three investigators unaware of the patient's anesthetic regimen. For the 15-min period of study we analyzed the ECG recordings for (a) maximum number of premature ventricular contractions (PVCs) per minute; (b) frequent PVCs (three or more per minute); (c) multifocal PVCs; (d) isorhythmic AV dissociation (progressive migration of the p wave toward and, eventually, into the QRS complex) (7–9); (e) changes in T-wave morphology (flattening or inversion); (f) ST depression or elevation (80 ms after the j point) and the degree (mm) of change in either; and (g) initial, minimum, and maximum heart rates. We also recorded the use of lidocaine to treat PVCs. The postoperative, 12-lead ECG was compared with the preoperative ECG for (a) changes in T-wave morphology; (b) ST depression or elevation and millimeter change in either; (c) the appearance of Q waves; and (d) the presence of ventricular ectopy.

Data were evaluated as incidences and mean values. Preoperative and postoperative values were compared using χ^2 analysis or Student's *t*-test. Logistic regression analyses were performed to determine whether ventricular ectopy, isorhythmic AV dissociations, or changes in ECG morphology were associated with aging or the combination of aging and N_2O. We accepted a value of $P < 0.05$ as significant.

Results

The anesthetic groups did not differ in age, gender, height, weight, preoperative use of β-sympathetic blocking drugs, or total dose of injected epinephrine (Table 1). Four patients given N_2O were ASA physical status III, whereas all patients given O_2 were ASA I or II. The preoperative incidence of cardiovascular disease was the same for each group. With one exception (see below), preoperatively and just before epinephrine injection all patients had a normal sinus rhythm.

Table 1. Patient Demographic and Clinical Characteristics

	N_2O	No N_2O
n	49	51
Age (yr)	39 ± 14	42 ± 15
No. of men	16 (32.6%)	14 (27.4%)
Height (cm)	66.5 ± 5.2	65.6 ± 3.5
Weight (kg)	76.6 ± 22.3	70.7 ± 14.3
ASA I or II	45 (91.8%)	51 (100%)[a]
Preoperative cardiovascular disease	15 (31%)	19 (37%)
β-Sympathetic blockers	2 (4%)	7 (14%)
Epinephrine injected (μg/kg)	2.52 ± 0.92	2.71 ± 0.89
Fentanyl (μg)	297 ± 133	283 ± 105
Isoflurane (% end-tidal)		
10–60 min of anesthesia	0.71 ± 0.30	0.86 ± 0.38[b]
>60 min of anesthesia	0.90 ± 0.29	1.08 ± 0.32[c]

N_2O, nitrous oxide.

All values are expressed as the number of patients displaying the indicated characteristic or (parametric values) as mean ± SD.

[a] $P = 0.037$ compared with the N_2O group.

[b] $P = 0.046$ compared with the N_2O group.

[c] $P = 0.008$ compared with the N_2O group.

Most aspects of anesthetic management were similar for both anesthetic groups, including premedication (equal fractions of each group received triazolam and morphine) and the total dose of fentanyl administered intraoperatively. However, more isoflurane was administered to patients who were not given N_2O.

Administration of epinephrine produced PVCs in several patients. However, the use of N_2O did not increase the incidence of PVCs from either a single focus or multiple foci (Table 2). Two patients, both given N_2O, required treatment with lidocaine for this arrhythmia.

The incidence of isorhythmic AV dissociation after injection of epinephrine was 50% higher in patients given N_2O (Table 2). Just before injection of epinephrine, one patient given N_2O developed isorhythmic AV dissociation, and dissociation was sustained throughout the 15-min period of recording. We included his data in our analysis as having had isorhythmic AV dissociation.

The heart rate response to epinephrine injection varied, increasing in some patients but decreasing in others (Table 3). The use of N_2O did not alter this response. Blood pressure changes associated with epinephrine injection did not differ between anesthetic

Table 2. Arrhythmias and Electrocardiographic Morphology Changes Associated With Epinephrine Injection

	N_2O *n* (%)	No N_2O *n* (%)
PVCs	10 (20.4)	8 (15.7)
>2 PVCs/min	8 (16.3)	4 (7.8)
Multifocal PVCs	4 (8.2)	3 (5.9)
Isorhythmic AV dissociation	30 (61.2)	21 (41.2)[a]
Intraoperative T-wave flattening and inversion	23 (46.9)	26 (50.9)
Postoperative T-wave flattening	23 (46.9)	19 (38.0)
Postoperative T-wave inversion	14 (29.2)	15 (29.4)

N_2O, nitrous oxide; *n*, number of patients; PVC, premature ventricular contraction; AV, atrioventricular.

[a] $P = < 0.05$ compared with the N_2O group.

Table 3. Peak Increase and Decrease in Heart Rate Response to Epinephrine

	N_2O	No N_2O
Baseline (beats/min)	85 ± 18	89 ± 16
Maximum increase (beats/min)	18 ± 13	19 ± 17
Maximum decrease (beats/min)	7 ± 8	8 ± 8

N_2O, nitrous oxide.

All values are expressed as mean ± SD.

groups, and isorhythmic AV dissociation was not associated with marked hypotension in any patient.

Postoperative changes in ECG morphology were common in both groups, but did not differ between groups. T-wave flattening occurred in 47% of patients given N_2O and in 38% of those not given N_2O. T-wave inversion occurred in 29% of patients in each group. Two patients given N_2O and one given O_2 had ST depression, the greatest change being 0.5 mm. No patient had new ventricular ectopy, ST elevation, or Q waves.

Neither aging nor N_2O alone correlated significantly with the development of ventricular ectopy, isorhythmic AV dissociation, or changes in ECG morphology after injection of epinephrine. However, in the presence of N_2O, logistic regression indicated that aging predisposed to the development of ventricular ectopy ($P < 0.01$) and was associated with a decreased incidence of T-wave flattening ($P < 0.05$).

Discussion

Like Wong et al., we found a trend suggesting that the use of N_2O augmented epinephrine's capacity to produce PVCs. Specifically, twice as many patients given N_2O had three or more PVCs per minute (16.3% ± 5.3% vs 7.8% ± 3.8%; mean ± SD). However, this trend did not approach statistical significance.

Our finding that N_2O may predispose to the development of isorhythmic AV dissociation extends that of Roizen et al. (3), who found that N_2O itself may produce isorhythmic AV dissociation (described in that work as AV junctional rhythm). Furthermore, our finding that epinephrine injection induces isorhythmic AV dissociation is consistent with the observation that these arrhythmias may be treated with propranolol (10). Our incidence of isorhythmic AV dissociation appears to be greater than that observed by Johnston et al. (for halothane, enflurane, or isoflurane) (11), but these investigators did not use N_2O nor did they monitor the ECG continuously for 15 min after epinephrine injection. Their period of examination ranged from 3 to 10 min. Clearly, the incidence of arrhythmias at the epinephrine dose levels administered (Table 1), with or without N_2O, is less than that reported for halothane (11). Other investigators have found isorhythmic AV dissociation in 40% of humans anesthetized with enflurane given with O_2 (12) and in 50% anesthetized with enflurane given with N_2O (13).

Despite the appreciable incidence of isorhythmic AV dissociation in our patients, the cardiovascular system remained stable with no marked hypotension in any patient, a finding consistent with the observations of others (12,13). Heart rate increased slightly with the onset of isorhythmic AV dissociation, an observation reported previously by others (7,9,13,14). Our results are consistent with the clinical impression of cardiovascular stability during anesthesia with N_2O (and isoflurane).

In designing this study, we debated whether to use O_2 or O_2 plus N_2 as the background gas for the patients not receiving N_2O. We selected O_2 because that is the usual choice of the clinician who decides not to apply N_2O. That is, we considered that the use of O_2 increased the clinical relevance of our results. For reasons of safety, the anesthetist charged with the patient's care had knowledge of the inspired concentration of O_2 given to the patient. However, all data collection and interpretation were performed by individuals who did not know whether the patient was or was not given N_2O. Thus we believe that the biases of the investigators did not influence the incidences of arrhythmias reported.

The simultaneous injection of lidocaine with epinephrine may have altered our results both for the comparison of the anesthetic groups (N_2O vs no N_2O) and the independent effect of epinephrine. Lidocaine decreases the arrhythmias produced by epinephrine injected in the presence of halothane (11). In addition, however, it may increase plasma levels of epinephrine by accelerating the rate of absorption of injected epinephrine (15).

Our two study groups differed in that the group given N_2O received less isoflurane, and the control group received a greater FIO_2. However, isoflurane is not known to have any antiarrhythmic effect (11), and the authors are unaware of evidence that hyperoxia predisposes to or protects the myocardium from the arrhythmic effects of epinephrine.

Postoperative T-wave flattening (47% in the N_2O group and 38% in the O_2 group) and inversion (29% in both groups) were common. These incidences are higher than those found by Breslow et al., who reported 12% for T-wave flattening and 6% for T-wave inversion ($P < 0.0001$ for both comparisons with our data) (16). There are at least two reasons for our finding a greater incidence of morphologic changes. First, catecholamine infusion may predispose to such changes. Predisposition is demonstrated by the nearly 50% incidence of postinjection T-wave changes in our patients and by similar results in other studies (17). Second, our patients had intracranial surgery, which has been associated with a relatively high incidence of such changes (18). However, it should be noted that at least one study failed to reveal an increased incidence after intracranial surgery (19). Because these changes occurred in our young and old patients alike, independent of cardiovascular disease state, they are likely to be innocuous. Such a conclusion ultimately agrees with that of Breslow et al. (16).

Forrest et al. reported that aging alone increases the incidence of ventricular ectopy (no injection of epinephrine) in awake and anesthetized subjects (Forrest, personal communication). We did not find an age-related increase in the incidence of arrhythmias associated with epinephrine injection. However, susceptibility to ventricular ectopy after epinephrine injection correlated with aging when anesthesia included N_2O. On the other hand, the nonspecific finding of T-wave flattening after epinephrine administration correlated inversely with aging, independent of the use of N_2O. The clinical significance of these findings is not clear.

We gratefully acknowledge the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny. Expert editorial assistance was provided by Winifred von Ehrenberg.

References

1. Smith NT, Eger EI II, Stoelting RK, Whayne TF, Cullen D, Kadis LB. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 1970;32:410–20.
2. Wong KC, Shaw CL, Blatnick RA. Epinephrine-induced dysrhythmias: the effect of nitrous oxide with halothane, enflurane, fluroxene or methoxyflurane. ASA abstracts of scientific papers, 1977:91–2.
3. Roizen MF, Plummer GO, Lichtor L. Nitrous oxide and dysrhythmias. Anesthesiology 1987;66:427–31.
4. Fleg JL. Alterations in cardiovascular structure and function with advancing age. Am J Cardiol 1986;57:33C–44C.
5. Christensen NJ Catecholamines and sympathetic nervous activity in the elderly. Acta Med Scan 1983;676(suppl):52–63.
6. Lakatta EG. Alterations in the cardiovascular system that occur in advanced age. Fed Proc 1979;38:163–7.
7. Schubart AF, Marriott HJL, Gorten RJ. Isorhythmic dissociation. Am J Med 1958;24:209–14.
8. Sethna DH, Deboer GE, Millar RA. Observations on "junctional rhythms" during anaesthesia. Br J Anaesth 1984;56:924–5.
9. Sosis M, Cooper PS, Herr G. The diagnosis of "junctional rhythms" with halogenated anesthetics. Anesthesiology 1985;63:233–4.
10. Hill RF. Treatment of isorhythmic A-V dissociation during general anesthesia with propranolol. Anesthesiology 1989;70:141–4.
11. Johnston RR, Eger EI II, Wilson C. Comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg 1976;55:709–12.
12. Calverley RK, Smith NT, Eger EI II. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 1978;57:619–28.
13. Haldemann G, Schaer H. Haemodynamic effects of transient atrioventricular dissociation in general anaesthesia. Br J Anaesth 1972;44:159–62.
14. Nishikawa T, Dohi S. Periodic isorhythmic dissociation during enflurane anesthesia in a patient with sinus bradycardia. J Anesth 1990;4:172–5.
15. Ueda W, Hirakawa M, Mori K. Acceleration of epinephrine absorption by lidocaine. Anesthesiology 1985;63:717–20.
16. Breslow MJ, Miller CF, Parker SD, Walman AT, Rogers MC. Changes in T-wave morphology following anesthesia and surgery: a common recovery-room phenomenon. Anesthesiology 1986;64:398–402.
17. Biberman L, Sarma RN, Surawicz B. T wave abnormalities during hyperventilation and isoproterenol infusion. Am Heart J 1971;81:166–73.
18. Rogers MC. Diagnosis and treatment of intraoperative cardiac dysrhythmias. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1986:499–521.
19. Morales R Jr, Shapiro WA, Donegan JH, et al. Electrocardiographic changes following neurosurgery. Anesthesiology 1987;67:A65.

Nitrous Oxide Does Not Impair Hepatic Function in Young or Old Surgical Patients

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LAMPE GH, WAUK LZ, WHITENDALE P, WAY WL, MURRAY W, EGER EI II. Nitrous oxide does not impair hepatic function in young or old surgical patients. Anesth Analg 1990;71:606–9.

We investigated whether anesthesia including nitrous oxide (N_2O) caused hepatic injury, and whether any adverse effect of N_2O was affected by patient age. One hundred patients having total hip replacements were randomly assigned to a regimen that included or excluded N_2O (50%–60%) during regional anesthesia supplemented with isoflurane and intravenous adjuvants. Using postoperative plasma levels of alanine aminotransferase, bilirubin, and alkaline phosphatase 1 and 3 days after surgery as indicators of hepatic impairment, we found no evidence that N_2O causes hepatic injury in either young or old patients.

Key Words: ANESTHETICS, GASES—nitrous oxide. LIVER, FUNCTION—nitrous oxide.

Limited evidence suggests that nitrous oxide (N_2O) may impair hepatic function. Plasma levels of the hepatic enzyme alanine aminotransferase (ALT, also known as SGPT) increase significantly more in patients anesthetized with halothane/N_2O at ambient pressure than they do in patients anesthetized with halothane/oxygen (O_2) in a hyperbaric chamber (1). Similarly, plasma levels of lactic dehydrogenase V increase in patients given methohexital and N_2O (2). At least one hepatic enzyme is damaged by administration of N_2O: exposure to 50%–70% N_2O for 3 h decreases hepatic methionine synthase activity in humans by 75% (3,4). Finally, Cohen et al. found evidence of hepatic injury in dentists and dental assistants exposed in the course of their occupation to high levels of N_2O (5,6).

Because N_2O is so often used in current clinical practice, we performed the following study to determine whether it impairs postoperative hepatic function. Additionally, we hypothesized that older patients might be more predisposed to hepatic injury (because they are at greater risk of cardiovascular compromise, more apt to take medications that affect hepatic function, and/or more likely to have a less balanced diet than younger patients). Accordingly, we also investigated whether aging or aging in concert with administration of N_2O might impair hepatic function.

Materials and Methods

One hundred patients scheduled for elective total hip arthroplasty consented to participate in our institutionally approved study. Preoperatively, we evaluated each patient for a history of hepatic disease and alcohol abuse (consumption of four or more ounces of alcohol per day). Sixty-five patients were to undergo initial total hip arthroplasty, and 35 required revision and replacement of a failed total hip arthroplasty. All patients received spinal (tetracaine, $n = 92$) or epidural (lidocaine, $n = 8$) anesthesia, and isoflurane, thiopental, and vecuronium, but were randomly assigned to receive in addition 60% N_2O/40% O_2 ($n = 50$) or 100% O_2 ($n = 50$). Premedications (triazolam, morphine, or none) and the intraoperative use of fentanyl and edrophonium/atropine were controlled by the attending anesthesiologist, not by the study protocol. Inhaled isoflurane concentrations were adjusted to maintain intraoperative systolic arterial blood pressure between 70 and 90 mm Hg. Median values for heart rate and arterial blood pressure were recorded for the following intervals of anesthetic

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Supported in part by PO1 AG03104A, the Anesthesia Research Foundation, and a grant from Anaquest, Inc.

Received from the Departments of Anesthesia and Orthopedics, University of California, San Francisco, California. Accepted for publication June 27, 1990.

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Table 1. Patient Demographic Characteristics

	N_2O	No N_2O
n	50	50
Age (yr)	60.2 ± 13.8	56.8 ± 17.2
Men (%)	38	48
Weight (kg)	72.8 ± 15.2	76.4 ± 15.0
ASA I or II (%)	90	88
ASA III (%)	10	12
Hepatic disease (%)	8	6
Alcohol abuse (%)	4	2

N_2O, nitrous oxide.
All values are expressed as mean ± SD or percentage of patients with the indicated characteristic.

delivery: 1–10 min, 11–60 min, and >60 min. We measured O_2 saturation (Ohmeda Biox II recording pulse oximeter) continuously for 24 h from the start of anesthesia in all patients. Intraoperatively, we adjusted F_{IO_2} to keep O_2 saturation above 90%. Episodes of desaturation to less than 86% were recorded.

We used plasma levels of ALT, an intracellular hepatic enzyme, as our primary marker of hepatic injury (7), but also measured plasma levels of bilirubin and alkaline phosphatase as markers of hepatic conjugative and secretory function. Venous blood samples were drawn immediately before surgery (control) and on postoperative days 1 and 3 for tests of hepatic function. All data collection, analysis, and patient interviews were performed by individuals unaware of whether the patient had received N_2O.

Data are reported as mean values, change, and percent change from preoperative values and evaluated for statistical significance using Student's *t*-test, analysis of variance, or χ^2 analysis. Logistic regression tests were performed to establish whether age, administration of N_2O, or the combined effects of age and N_2O affected hepatic integrity. We accepted as significant a value of $P < 0.05$.

Results

The two study groups did not differ in age, gender, weight, ASA physical status, incidence of hepatic disease, or heavy alcohol consumption (Table 1). Aspects of anesthetic management that were similar for each group included drugs used for premedication, duration of anesthesia, mean and lowest intraoperative systolic blood pressure (first 10 min, 11–60 min, or 60 min to end) and frequency of intraoperative or postoperative O_2 saturation <86% (Table 2). The groups differed in that greater doses of thiopental, fentanyl, and isoflurane were administered to patients who did not receive N_2O.

Table 2. Variables Associated With Anesthesia

	N_2O	No N_2O
Premedication		
Triazolam	74	74
Morphine	58	42
Thiopental (mg)	364 ± 131	443 ± 197[a]
Fentanyl (μg)	146 ± 105	220 ± 139[a]
Vecuronium (mg)	8.0 ± 3.1	8.5 ± 2.4
Maintenance end-tidal isoflurane (%)		
11–60 min	0.39 ± 0.23	0.54 ± 0.29[b]
>60 min	0.41 ± 0.21	0.64 ± 0.27[b]
Duration of anesthesia (min)	190 ± 23	204 ± 60
Mean systolic blood pressure (mm Hg)		
First 10 min	120 ± 23	121 ± 24
11–60 min	93 ± 13	95 ± 10
>60 min	94 ± 13	96 ± 14
Lowest systolic blood pressure (mm Hg)		
First 10 min	92 ± 23	96 ± 23
11–60 min	78 ± 12	80 ± 9
>60 min	75 ± 10	78 ± 12
Oxygen saturation <86%		
Intraoperative	7.0	2.3
Postoperative	27.9	27.2

N_2O, nitrous oxide.
Values are expressed as percentage of patients with the indicated characteristic or mean ± SD.
[a] $P \le 0.02$.
[b] $P \le 0.01$.

Four patients received 50% N_2O, and 46 received 60%. In one patient who became hypoxic intraoperatively, we discontinued the administration of N_2O and maintained anesthesia with isoflurane in O_2. The data for this patient are included with the data for the group given N_2O.

The absolute and percent change in ALT, bilirubin, and alkaline phosphatase levels from preoperative to maximal postoperative values were similar in each anesthetic group (Table 3). The maximum changes tended to be negative, rather than positive, but varied considerably. Nine patients (six given N_2O) had preoperative ALT levels above the upper limit of normal set by our laboratory (normal range, 2–54 IU/L). All but one of these patients had normal postoperative ALT levels. The one patient whose values did not return to normal had a preoperative value of 199 IU/L and a postoperative value of 77 IU/L. Five patients (three given N_2O) having normal baseline levels had abnormal postoperative levels.

Baseline and postoperative bilirubin values were normal in all patients but one given O_2, who developed an abnormal postoperative level. Only one patient had an abnormal baseline value for alkaline phosphatase, whereas four patients (three given

Table 3. Perioperative Hepatic Function

	N_2O	No N_2O
ALT (IU)		
Preoperative	25.8 ± 36.9	19.7 ± 15.9
Postoperative day 1	19.3 ± 21.4	31.2 ± 79.4
Postoperative day 3	27.3 ± 71.7	19.5 ± 21.7
Maximum change[a]	−10.2 ± 29.8	−3.6 ± 22.7
Bilirubin (mg/dL)		
Preoperative	0.57 ± 0.16	0.56 ± 0.24
Postoperative day 1	0.65 ± 0.20	0.68 ± 0.24
Postoperative day 3	0.57 ± 0.13	0.57 ± 0.26
Maximum change	−0.03 ± 0.14	−0.05 ± 0.18
Alkaline phosphatase (IU)		
Preoperative	71.3 ± 22.2	65.8 ± 21.1
Postoperative day 1	57.8 ± 18.0	55.1 ± 22.4
Postoperative day 3	75.6 ± 41.9	66.8 ± 27.2
Maximum change	−13.9 ± 14.5	−11.9 ± 14.4

ALT, alanine aminotransferase.
Values are expressed as mean ± SD.
[a] The average greatest change from the preoperative value.

N_2O) with appropriate baseline levels developed abnormal postoperative levels. These four patients also had abnormal postoperative levels of ALT.

As indicated above, one patient had intraoperative hypoxemia that persisted more than 1 min and required intervention. This patient had an increased baseline ALT level that did not return to normal levels postoperatively, but had normal bilirubin and alkaline phosphatase levels throughout the study.

None of the changes in hepatic function were clinically significant in any patient. None prolonged hospitalization. Neither aging nor the combination of aging and N_2O predisposed to the development of hepatic injury.

Discussion

Our findings do not confirm those that suggest that N_2O administration might result in hepatic injury. That is, we found no correlation between administration of N_2O and the development of injury. Although ALT, bilirubin, and alkaline phosphatase levels increased in a small number of our patients, these changes were independent of the use of N_2O or O_2. The absence of any consistent trend in outcomes in our study (see Table 3) associating N_2O with hepatic injury suggests that a larger database would not provide a different result.

Ten patients (10%) had preoperative evidence of existing hepatic injury (increased serum transaminase levels), but the incidence of this evidence of hepatic injury actually decreased after anesthesia and surgery. That is, the "stress" of anesthesia and surgery, with or without N_2O, also did not predispose to hepatic injury. Similarly, patients with a history of hepatic disease or alcohol abuse were not more likely to have an increase in ALT levels postoperatively. The finding for alcohol abuse confirms that noted by Zinn et al. (8).

Despite general concerns regarding the use of N_2O, it remains a mainstay of anesthetic practice. Although reassuring, our findings may not be definitive for three reasons. First, we obtained and examined results from a study of a relatively limited number of patients (n = 100). Second, we cannot say that more prolonged or traumatic surgery, greater age, and/or more severe hypotension would not predispose patients to hepatic injury when combined with administration of N_2O. However, no trend in our data suggests such an outcome. Third, our two groups differed in that the group given N_2O received less thiopental, fentanyl, and isoflurane. It is possible that these agents have a mild hepatotoxic effect that confounded our results. However, on average, the incidence of abnormal postoperative ALT values *decreased* (not significantly), suggesting that none of the agents or techniques compromised hepatic function.

The strength of our findings lies in the comparability of our study groups (equivalence of age, sex, operative stress). Total hip replacement is a longer, more traumatic procedure than many other surgeries, demanding greater blood replacement than most other surgeries. Our study population included older patients, and our anesthetic regimen deliberately imposed hypotension to decrease blood loss (9). We expected that these conditions would predispose our patients to a subtle noxious effect of N_2O, yet none was demonstrated.

Finally, N_2O may cause hypoxia by limiting the inspired fraction of O_2, and hypoxia can cause hepatic injury (10). The only patient to develop intraoperative hypoxia received N_2O, and the hypoxia resolved after substitution of O_2 for N_2O. Although this patient's hepatic function was not adversely affected, failure to detect and reverse intraoperative hypoxemia may account for some cases of postoperative hepatic dysfunction after an anesthetic that includes N_2O.

We gratefully acknowledge the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny. Expert editorial assistance was provided by Winifred von Ehrenberg.

References

1. Pratilas V, Pratilas MG, Bramis J, Smith H Jr. The hepatoprotective effect of oxygen during halothane anesthesia. Anesth Analg 1978;57:481–5.
2. Prys-Roberts C, Sear JW, Low JM, Phillips KC, Dagnino J. Hemodynamic and hepatic effects of methohexital infusion during nitrous oxide anesthesia in humans. Anesth Analg 1983;62:317–23.
3. Koblin DD, Waskell L, Watson JE, Stokstad ELR, Eger EI II. Nitrous oxide inactivates methionine synthetase in human liver. Anesth Analg 1982;61:75–8.
4. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. Anesthesiology 1988;68:213–6.
5. Brodsky JB. Toxicity of nitrous oxide. In: Eger EI II, ed. Nitrous oxide/N_2O. New York: Elsevier, 1985:259–79.
6. Cohen EN, Brown BW, Wu ML, et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980;101:21–31.
7. Isselbacher KJ, LaMont JT. Diagnostic procedures in liver disease. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. Harrison's principles of internal medicine. New York: McGraw-Hill, 1983:1779–84.
8. Zinn SE, Fairley HB, Glenn JD. Liver function in patients with mild alcoholic hepatitis, after enflurane, nitrous oxide-narcotic, and spinal anesthesia. Anesth Analg 1985;64:487–90.
9. Thomson GE, Miller RD, Stevens WC, Murray WR. Hypotensive anesthesia for total hip arthroplasty. Anesthesiology 1978;48:91–6.
10. Shingu K, Eger EI II. Johnson BH. Hypoxia per se can produce hepatic damage without death in rats. Anesth Analg 1982;61:820–3.

Effect of Nitrous Oxide on Folate and Vitamin B_{12} Metabolism in Patients

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KOBLIN DD, TOMERSON BW, WALDMAN FM, LAMPE GH, WAUK LZ, EGER EI II. Effect of nitrous oxide on folate and vitamin B_{12} metabolism in patients. Anesth Analg 1990;71:610–7.

Exposure to nitrous oxide (N_2O) markedly enhances excretion of formic acid and formiminoglutamic acid (FIGLU) in the urine of rats, suggesting a disruption in the normal pathways of folic acid metabolism secondary to an N_2O-induced inactivation of methionine synthase. We tested whether surgical patients (23 having total hip replacements and 26 having resection of acoustic neuromas) exposed to isoflurane alone or combined with N_2O responded similarly. We found no increase in urinary formic acid and FIGLU in patients exposed to N_2O for hip replacement, but a small, transient increase in the FIGLU-to-creatinine ratio in those undergoing resection of acoustic neuromas (mean duration of anesthesia = 9.3 h). This increase peaked at the end of anesthetic exposure and returned toward control levels by the first day after anesthesia and surgery. Low preoperative levels of red blood cell folate and low-normal levels of serum vitamin B_{12} did not predict an increase in formic acid or FIGLU in response to N_2O. Although an occasional patient may prove highly susceptible to and develop signs of severe vitamin B_{12} and folic acid deficiency after exposure to N_2O, our findings suggest that this is a rare event.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—isoflurane. VITAMINS—B_{12}, folic acid.

Patients occasionally develop hematologic and neurologic abnormalities after surgery with an anesthetic technique that includes the administration of nitrous oxide (N_2O) (1,2). For example, those with subclinical deficiencies of vitamin B_{12} may have neurologic dysfunction and manifest megaloblastic changes after routine surgical procedures with a duration of approximately 2 h (3,4). Even relatively healthy patients without vitamin B_{12} or folic acid deficiency may experience bone marrow depression after prolonged (24 h) exposure to N_2O (5,6). Presumably, these abnormalities result from N_2O-induced inactivation of the vitamin B_{12}-dependent enzyme methionine synthase (EC 2.1.1.13), an enzyme that controls interrelations between vitamin B_{12} and folic acid metabolism.

In humans, methionine synthase activity in liver decreases by approximately 50% after 1–2 h of exposure to 50%–70% N_2O (7,8). However, the data indicating the temporal course of changes in vitamin B_{12} and folic acid metabolism, and of enzyme inactivation and recovery, are limited. Assay of this cytoplasmic enzyme requires biopsies of vital tissues (e.g., liver, kidney, brain) that are difficult to perform in human subjects. Thus, it would be useful to have a noninvasive method of monitoring the metabolic activities of these vitamins in response to N_2O.

Studies in rats suggest that the levels of formic acid (9) and formiminoglutamic acid (FIGLU) (10) excreted in urine may reflect the status of folate metabolism. The ratio of formic acid-to-creatinine in urine increases as much as 40-fold in rats exposed to N_2O (9), and the concentration of FIGLU is markedly higher than normal (10). Accordingly, we have measured the levels of formic acid and FIGLU in the urine of two groups of patients exposed to N_2O. The first group included elderly patients having total hip replacements, whose age predisposes to deficiencies in

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Supported in part by NIA grant PO1 AG3104, by a grant from the Academic Senate of the University of California of San Francisco, and by the Anesthesia Research Foundation.

Received from the Department of Anesthesia, Veterans Administration Medical Center, San Francisco, California, and the Departments of Anesthesia and Laboratory Medicine, University of California, San Francisco, California. Accepted for publication July 2, 1990.

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vitamin B_{12} and/or folate (11–13); the second group included patients undergoing resection of acoustic neuromas, a procedure that usually requires the prolonged administration of anesthetic. The enhanced excretion of formic acid and FIGLU in rats probably is due to N_2O-induced inactivation of methionine synthase and the resulting depletion of active forms of tetrahydrofolate required for the further oxidation of formic acid to carbon dioxide (9) and metabolism of FIGLU (a breakdown product of histidine) to glutamate (10). We hypothesized that our two groups of patients would experience similar metabolic abnormalities.

Table 1. Patient Demographic Characteristics

	Hip replacements		Acoustic neuromas	
	N_2O	No N_2O	N_2O	No N_2O
n	12	11	13	13
Age (yr)	66 ± 12.5	64 ± 9.3	50 ± 10.8	48 ± 10.2
Male (*n*)	3	5	10	8
Weight (kg)	69 ± 13.3	80 ± 14.6	79 ± 13.9	80 ± 15.8
ASA I or II	11	9	12	11
ASA III	1	2	1	2

N_2O, nitrous oxide.
Values are given as numbers of patients, or as mean ± SD.

Materials and Methods

With approval from the University of California at San Francisco (UCSF) Committee on Human Research and patients' informed consent, we studied 23 people having elective total hip arthroplasty and 26 undergoing elective resection of acoustic neuroma at the UCSF Moffitt and Long Hospitals. All patients received isoflurane, thiopental, and vecuronium, but were randomly assigned to receive either 50%–70% N_2O or 100% oxygen. Premedication (triazolam and/or morphine or nothing) and intraoperative administration of fentanyl and edrophonium/atropine were controlled by the anesthesiologist. Inhaled isoflurane concentrations were adjusted to maintain clinically acceptable levels of anesthesia, as determined by the anesthesiologist in charge of the patient's care. Patients undergoing total hip arthroplasty also received spinal (tetracaine) or epidural (lidocaine) anesthesia. Duration of anesthesia was 2.0–6.5 h for the total hip arthroplasties and 5–16 h for resection of acoustic neuromas. Intraoperative and postoperative blood transfusions were administered as clinically required, as determined by the physician in charge of the patient's care.

Preoperative blood samples were drawn and assayed for serum vitamin B_{12}, serum folate, and red blood cell (RBC) folate. Additional blood samples were obtained on postoperative day 1 in the patients undergoing resection of acoustic neuromas. A spot urine sample was collected preoperatively. In patients undergoing total hip arthroplasties, spot urine samples also were collected in the recovery room, on postoperative days 1–3, and with less frequency on days 6, 9, 11, and 13. From patients undergoing resection of acoustic neuromas, we collected urine samples via a Foley catheter at a time estimated to be the midpoint of surgery, at the end of anesthesia, and on postoperative days 1 and 2. Serum and urine samples were frozen at −20°C to −40°C until analyzed.

Urinary FIGLU was analyzed by the spectrophotometric procedure specified in Sigma Diagnostics Procedure No. 365-UV. Urinary creatinine was assessed spectrophotometrically using a Sigma Diagnostics Creatinine Kit (Procedure No. 555). Urinary formic acid was analyzed by the spectrophotometric method used for formic acid in serum (14), excluding the acetonitrile precipitation step because it was not necessary.

Serum levels of vitamin B_{12} and folate, and red cell folate, were determined in duplicate by a radioassay (MAGIC Vitamin B_{12} [^{57}Co]/Folate[^{125}I] No Boil Radioassay [CIBA-Corning Diagnostics]) that utilizes purified intrinsic factor for analysis of vitamin B_{12}. Using this assay, serum levels of these vitamins in a low folate/vitamin B_{12} control (BioRad) and in clinical chemistry controls (Ligand A, B, C; CIBA-Corning) were within the expected range. The range of vitamin levels considered to be normal were those specified in the CIBA-Corning No Boil Radioassay kit.

The data were examined as mean values and change and percentage change from preoperative values using paired or unpaired *t*-tests, the Mann–Whitney test, or Fisher's exact test (all two-tailed tests). Regression analyses were performed to test for a relationship between age and levels of serum vitamin B_{12}, serum folate or RBC folate, or a relationship between these variables and maximal elevation of the FIGLU-to-creatinine ratio in urine.

Results

Demographic characteristics did not differ significantly in patients anesthetized with and without N_2O (Table 1). Preoperative levels of serum vitamin B_{12} (Figure 1A), serum folate (Figure 1B), and RBC folate (Figure 1C) also did not differ among patients (Table 2). No patient was deficient in vitamin B_{12} (normal

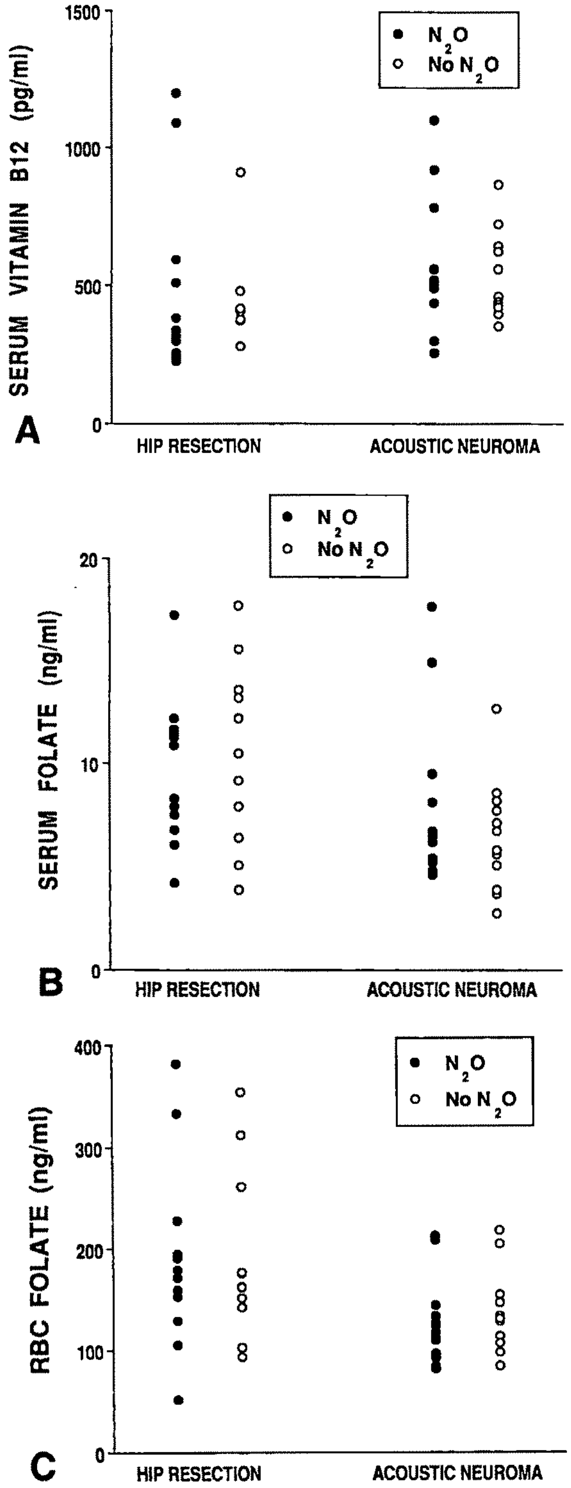

Figure 1. Preoperative levels of serum vitamin B_{12} (A), serum folate (B), and RBC folate (C) in patients having total hip replacements and resections of acoustic neuromas. For the radioassay employed, recommendations for normal ranges are 200–978 pg/mL for serum vitamin B_{12}, 3.0–15.0 ng/mL for serum folate, and 130–630 ng/mL for RBC folate. Some symbols overlap.

Table 2. Preoperative Vitamin Levels

	Hip replacements		Acoustic neuromas	
	N_2O	No N_2O	N_2O	No N_2O
Serum B_{12} (pg/mL)	472 ± 320	421 ± 168	568 ± 226	518 ± 148
Serum folate (ng/mL)	9.6 ± 3.4	10.5 ± 4.2	7.6 ± 4.0	6.4 ± 2.5
RBC folate (ng/mL)	190 ± 87	192 ± 79	126 ± 40	144 ± 41

N_2O, nitrous oxide; RBC, red blood cell.
Values are mean ± SD.

range, 200–978 pg/mL for this assay) or had abnormally low serum folate values (normal range, 3.0–15.0 ng/mL). However, 4 of the 23 patients having total hip replacements and 15 of 26 (a surprisingly high proportion) having resection of acoustic neuromas had low RBC folate values (normal range, 130–630 ng/mL) (Figure 1C). Weak but significant correlations were found between age and serum vitamin B_{12} ($R = -0.411$; $P = 0.0034$), age and serum folate ($R = 0.367$; $P = 0.0095$), and age and RBC folate ($R = 0.412$; $P = 0.0032$).

Aspects of anesthetic management, including the duration of anesthesia, were similar for the groups given and not given N_2O (Table 3). However, in patients not given N_2O, those having total hip replacements received less morphine and more thiopental, and both surgical populations required higher end-tidal concentrations of isoflurane (at times >60 min) (Table 3).

The ratios of formic acid-to-creatinine in urine (Figure 2) and FIGLU-to-creatinine (Figure 3) did not differ significantly between patients anesthetized with and without N_2O for total hip replacement. However, an 85-yr-old woman given 60% N_2O for 3.0 h (preoperative serum vitamin B_{12} level of 319 pg/mL, serum folate of 6.8 ng/mL, and RBC folate of 160 ng/mL) exhibited a 10-fold increase in the formate-to-creatinine ratio in the recovery room after anesthesia (Figure 4A), and a fivefold increase in the FIGLU-to-creatinine ratio on postoperative day 2 (Figure 4B).

In patients undergoing resection of acoustic neuromas (Figure 5), the ratios of formic acid-to-creatinine in urine did not differ between anesthetic groups at any time. However, the ratios of FIGLU-to-creatinine increased after induction of anesthesia in most (but not all) patients exposed to N_2O, and were significantly ($P = 0.0057$) greater than the preoperative values at the end of anesthesia (Figure 6). In contrast, patients not given N_2O tended to have lower FIGLU-to-creatinine ratios than the N_2O group, with a significant ($P = 0.0063$) decrease from baseline at the operation's midpoint (Figure 6). Values returned toward baseline by postoperative day 1 (Figure 6).

Table 3. Variables Associated With Anesthesia

	Hip replacements		Acoustic neuromas	
	N_2O	No N_2O	N_2O	No N_2O
Premedication				
Triazolam (*n*)	6	9	2	0
Morphine (*n*)	5	0[a]	1	0
Thiopental (mg)	300 ± 103	493 ± 226[b]	500 ± 220	470 ± 170
Fentanyl (μg)	96 ± 101	200 ± 152	1000 ± 520	1450 ± 910
Vecuronium (mg)	6.8 ± 2.9	6.1 ± 4.3	13.5 ± 5.3	14.3 ± 5.1
Maintenance end-tidal isoflurane (%)				
10–60 min	0.38 ± 0.24	0.43 ± 0.11	0.53 ± 0.29	0.58 ± 0.24
>60 min	0.32 ± 0.11	0.49 ± 0.19[b]	0.85 ± 0.15	1.09 ± 0.28[b]
Duration of anesthesia (h)	3.0 ± 0.8	3.6 ± 1.2	9.3 ± 2.4	9.9 ± 3.8

N_2O, nitrous oxide.
Values are given as numbers of patients or mean ± SD.
[a] Value in the no-N_2O group significantly less than value in the N_2O group at $P < 0.05$, using Fisher's exact test.
[b] Values in the no-N_2O group significantly greater than values in the N_2O group at $P < 0.02$, using unpaired *t*-tests.

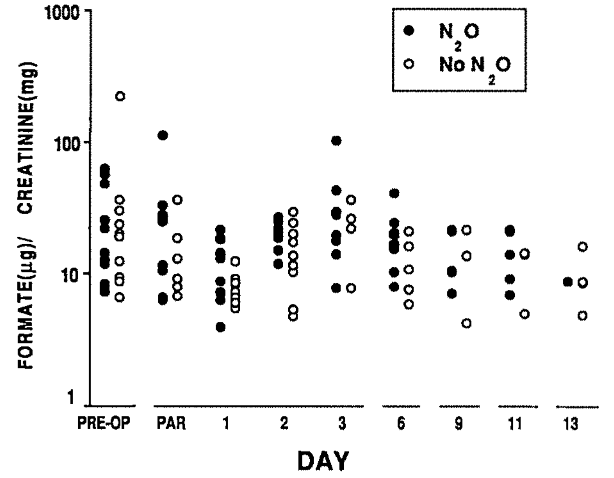

Figure 2. Ratios of formic acid to creatinine in urine in patients having total hip replacements did not increase as a consequence of exposure to N_2O (*closed circles*). Samples were obtained before anesthesia (PRE-OP), in the recovery room after anesthesia (PAR), and on days 1, 2, 3, 6, 9, 11, and 13 after anesthesia and surgery. The *open circles* represent values obtained in patients who did not receive N_2O. Some symbols overlap.

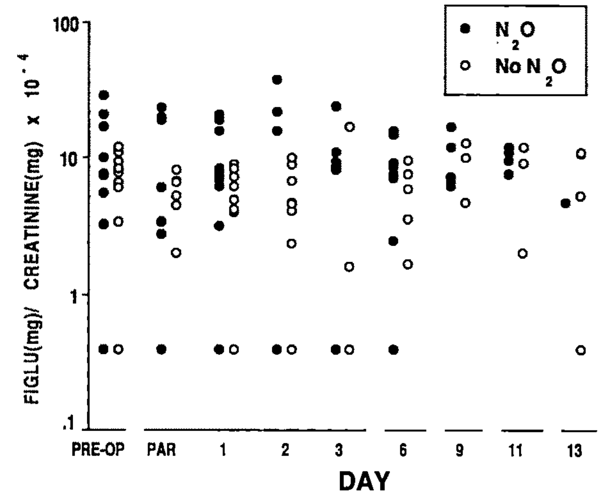

Figure 3. Ratios of FIGLU to creatinine in urine in patients having total hip replacements did not increase as a consequence of exposure to N_2O (*closed circles*). The *open circles* represent values obtained in patients who did not receive N_2O. For clarity of presentation on the logarithmic scale, ratios of 0.4×10^{-4} or less are represented as 0.4×10^{-4}. Some symbols overlap.

Serum vitamin B_{12} levels did not change on postoperative day 1 in either anesthetic group having resection of acoustic neuromas (Table 4, Figure 7). Serum folate levels tended to increase on the first postoperative day in patients exposed to N_2O, but they decreased in those not exposed (Table 4, Figure 7). Red blood cell folate levels increased on postoperative day 1 in all patients except one, independent of exposure to N_2O (Table 4, Figure 7).

Discussion

The large increases in formic acid (9) and FIGLU (10) excretion in the urine of rats exposed to N_2O probably result from inactivation of methionine synthase and consequent intracellular depletion of active forms of tetrahydrofolate required for the enzymatic oxidation of formic acid to carbon dioxide (9) and catabolism of FIGLU (10,15). Our results demonstrate that excretion of these compounds in humans is less severely affected by N_2O. Several possibilities might explain these species differences. First, inactivation of hepatic methionine synthase is slower in humans (half-time for inactivation, 1–2 h) (7,8) than in rodents (half-time for inactivation, 5–15 min) (8,16,17). However, the duration of exposure to N_2O in our patients should have resulted in >90% inactivation of enzyme (Table 3). Second, humans may have sufficient tissue levels of active tetrahydrofolate derivatives to permit

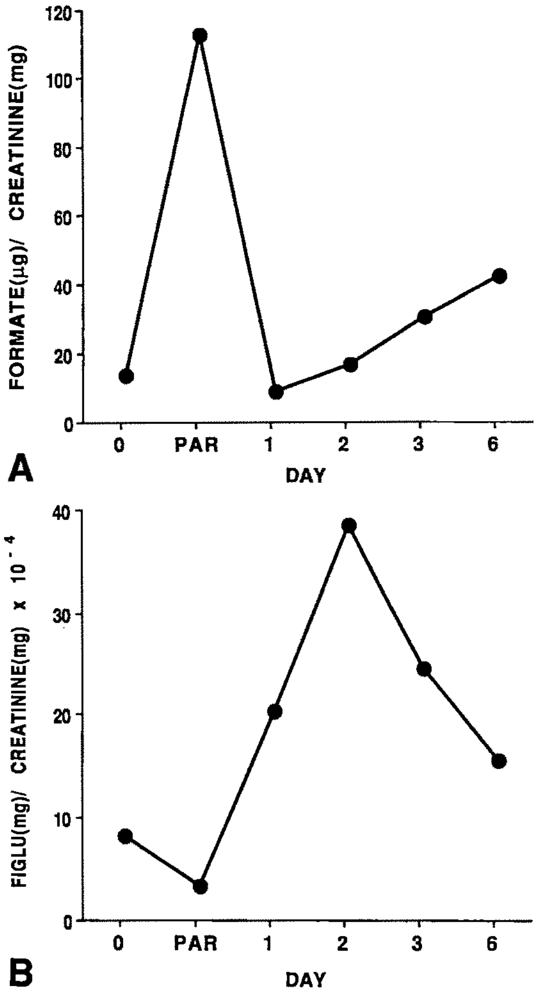

Figure 4. Formic acid- (A) and FIGLU- (B) to-creatinine ratios in urine increased in an 85-yr-old woman given 60% N_2O for 3 h during total hip replacement. Note that the ordinate in this graph is linear, whereas the ordinates in Figures 2 and 3 are logarithmic.

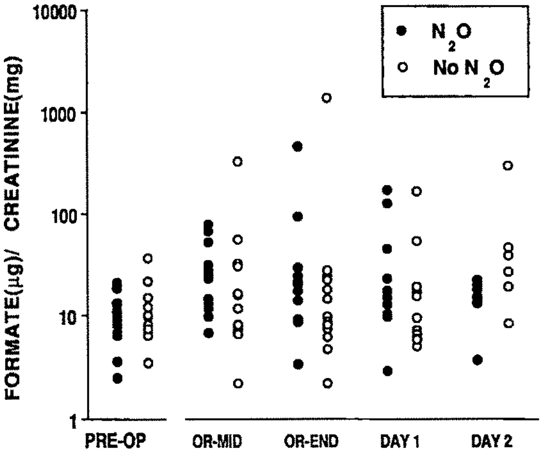

Figure 5. Ratios of formic acid to creatinine in urine did not increase in patients anesthetized with N_2O (*closed circles*) relative to those anesthetized without N_2O (*open circles*) for resection of acoustic neuromas. Urine samples were obtained before anesthesia (PRE-OP), at the approximate midpoint of the operation (OR-MID), at the end of the operation (OR-END), and on days 1 and 2 after anesthesia and surgery. Some symbols overlap.

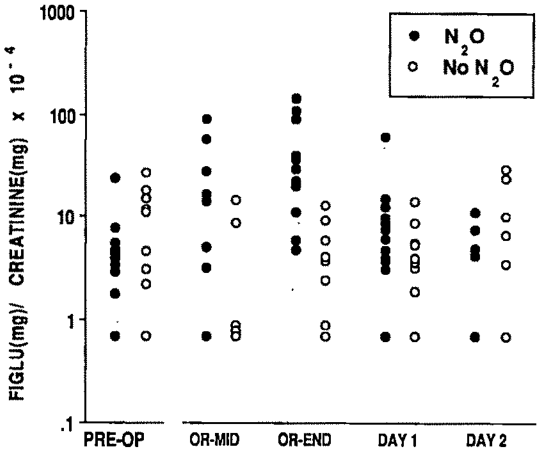

Figure 6. Ratios of urinary FIGLU to creatinine in patients having resection of acoustic neuromas increased at the end of the operation (OR-END) in patients given N_2O (*closed circles*) compared with those not given N_2O (*open circles*) ($P < 0.001$; Mann–Whitney test), and compared with values obtained before anesthesia (PRE-OP) ($P = 0.0057$; paired *t*-test). For clarity of presentation on the logarithmic scale, ratios of 0.7×10^{-4} or less are represented as 0.7×10^{-4}. Some symbols overlap.

metabolism of formic acid and FIGLU, even after marked inactivation of methionine synthase. Although possible, this explanation is less likely because rodents have higher hepatic tetrahydrofolate and formyltetrahydrolate levels than humans (18). Third, rodents and humans may differ in the way they produce, use, and/or eliminate formic acid and FIGLU.

Although our patients demonstrated no extreme increases in formic acid and FIGLU excretion, the ratios of urinary FIGLU-to-creatinine increased in most (but not all) patients given N_2O for resection of acoustic neuromas (Figure 6). The FIGLU-to-creatinine ratio maximally increased 10-fold at the end of anesthetic exposure, but returned to control levels by the first postoperative day (Figure 6), implying a rapid reversal of any perturbation in folate metabolism caused by N_2O. This finding suggests that relatively long exposure to N_2O (Table 3) transiently depletes cellular forms of active tetrahydrofolate in humans, thereby interfering with the breakdown of FIGLU.

In a preliminary study of six healthy, young adult volunteers exposed to 1.5 atm N_2O for 2.2–4.9 atm-h who received daily oral loading doses of histidine for 5 days after N_2O exposure, Hawkins et al. (19) found that urinary excretion of FIGLU increased approximately twofold in two of the six subjects. Combined,

Table 4. Values for Serum B_{12}, Serum Folate, and Red Blood Cell Folate in Acoustic Neuroma Patients, Postoperative Day 1

	N_2O	No N_2O
Serum B_{12}	1.2 ± 12.4	−0.1 ± 10.9
Serum folate	10.2 ± 25.2	−22.2 ± 24.7[a]
RBC folate	30 ± 31.5[b]	62 ± 52.6[b]

N_2O, nitrous oxide; RBC, red blood cell.

Values expressed as percent change from preoperative values, and are given as mean ± SD.

[a] Significantly different from the N_2O group, $P = 0.005$, by Mann–Whitney test.

[b] Significantly greater than preoperative value, $P < 0.005$, by paired t-tests.

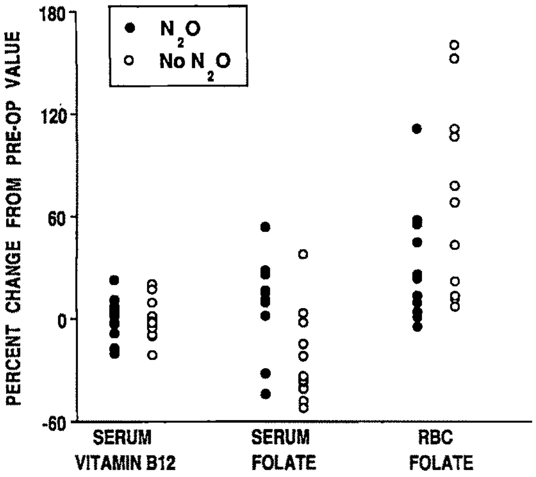

Figure 7. As a percentage of control values obtained before anesthesia, serum vitamin B_{12} and folate and RBC folate levels obtained the day after resection of acoustic neuromas either did not change (serum vitamin B_{12}), increased ($P = 0.005$; Mann–Whitney test) in patients given versus not given N_2O (serum folate), or increased ($P < 0.005$; paired t-tests) regardless of N_2O administration (RBC folate). Some symbols overlap.

these results and ours imply that humans may develop a mild, transient functional folic acid deficiency after more than 3 atm-h of exposure to N_2O.

No patient in either surgical group had abnormally low preoperative values for serum vitamin B_{12} or folic acid (Figures 1A, 1B). However, preoperative RBC folate levels, which are a better indicator of folate tissue stores (20), were low (<130 ng/mL) in 17% (4/23) of patients having total hip replacements. This percentage is within the 5%–60% range of elderly patients reported to be deficient in RBC folate (21). An unexpected finding was that 15/26 (58%) patients (9/15 anesthetized with N_2O) undergoing resection of acoustic neuromas also were deficient in RBC folate, and many of the remaining patients had low-normal levels. These low values in this selective surgical population could not be attributed to the effects of medications given before surgery.

Changes in serum and RBC folate levels after anesthesia in patients having resection of acoustic neuromas (Table 4, Figure 7) were consistent with previously reported trends. The higher levels of serum folate in patients given N_2O confirm earlier findings in both animals and humans. That is, plasma folate levels increase approximately twofold in rats after an 8-h exposure to 50% N_2O (22), and serum folate levels increase similarly in vascular surgery patients exposed to 70% N_2O for 24 h (23). The lower levels of serum folate we found on postoperative day 1 in those anesthetized without N_2O also reiterate previous findings (23). The mechanism underlying increased serum folate levels after N_2O exposure is not known, but may be related to impaired hepatic uptake of folate (24). It is also unclear why RBC folate content would increase 1 day after anesthesia and surgery independently of exposure to N_2O (Table 4, Figure 7). This finding does not appear to be related to perioperative administration of blood or vitamins, because transfusions were given to only 4/26 acoustic neuroma patients and only two patients were known to receive vitamin supplements.

Serum vitamin B_{12} levels in patients undergoing resection of acoustic neuromas did not change on the first postoperative day, independent of exposure to N_2O (Table 4, Figure 7). Previous results have also shown no change in serum vitamin B_{12} levels 24 h after >4 h of exposure to 66% N_2O in oxygen and halothane (25), or at the end of a 24-h administration of N_2O to three patients undergoing surgery for repair of aortic aneurysms (26).

None of the 49 patients examined in this study (25 of whom received N_2O) exhibited extreme or persistent elevations in the excretion of formic acid or FIGLU in urine, suggesting that a severe functional deficiency in folic acid did not occur. In addition, the levels of vitamins in the blood did not correlate with the maximal elevation in formic acid or FIGLU. Indeed, some elderly individuals with a deficiency in RBC folate and low-normal levels of serum vitamin B_{12} received N_2O without an apparent effect on folate metabolism. For example, a 73-yr-old man with a preoperative serum vitamin B_{12} level of 236 pg/mL and a RBC folate of 51 ng/mL was given 60% N_2O for 4.5 h, and a 72-yr-old woman with a serum vitamin B_{12} level of 229 pg/mL and RBC folate of 105 ng/mL was given 60% N_2O for 2.8 h without demonstrating enhanced excretion of formic acid or FIGLU in urine. Although an occasional patient may be highly susceptible to the disruptive effect of N_2O on folate metabolism (3,4), this would appear to be a rare event. One elderly woman who received N_2O for 3 h (Figure 3) had transient elevations in formic acid and

FIGLU levels in urine. However, the smallness and transience of the changes observed probably indicate only a mild functional deficiency in folic acid. Furthermore, the absence of significant neurologic (27) or hematologic (28) abnormalities or other adverse outcomes (29) in these patients suggests that these effects do not have toxic consequences.

A limitation of the present study is that long-term follow-up of these patients was not performed. The possibility remains that some patients might develop signs and/or symptoms of vitamin B_{12} or folate deficiency at times quite removed from the acute exposure to N_2O. For example, in the case reports of Schilling (3) and Berger et al. (4), symptoms of vitamin B_{12} deficiency appeared 1–5 mo after N_2O exposure. The mechanism behind such a delayed action of N_2O is unclear, but it is conceivable that certain patients may exhibit a very slow de novo synthesis of methionine synthase after N_2O inactivation, have enough stores of active folate to continue normal metabolic processes involving vitamin B_{12} and folate for a limited time period, and then eventually become depleted of active tissue folate. However, because most animal and human studies have shown the N_2O-induced perturbation in vitamin B_{12} and folate metabolism to revert toward normal after removal of N_2O, we believe this explanation is unlikely.

In summary, the marked elevations of urinary formic acid and FIGLU that are observed in rats after exposure to N_2O are not found in patients, even after prolonged exposure to N_2O. Transient elevations in the excretion of FIGLU in urine may be found in some patients after N_2O exposure, suggestive of a mild functional deficiency in folic acid, but one without clinical consequences.

The authors thank John Osterloh, MD, for his help and advice concerning the assay for formic acid.

References

1. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B_{12}. Br J Anaesth 1987;59:3–13.
2. Nunn JF. Clinical relevance of the B_{12}/N_2O interaction. Anaesthesia 1988;43:587–9.
3. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12}-deficient subjects? JAMA 1986;255:1605–6.
4. Berger JJ, Modell JH, Sypert GW. Megaloblastic anemia and brief exposure to nitrous oxide—a causal relationship? Anesth Analg 1988;67:197–8.
5. Amess JAL, Burman JF, Rees GM, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 1978;ii:339–42.
6. Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. Br J Haematol 1983;53:189–200.
7. Koblin DD, Waskell L, Watson JE, Stokstad ELR, Eger EI II. Nitrous oxide inactivates methionine synthetase in human liver. Anesth Analg 1982;61:75–8.
8. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. Anesthesiology 1988;68:213–6.
9. Black KA, Virayotha V, Tephly TR. Reduction of hepatic tetrahydrofolate and inhibition of exhalation of $^{14}CO_2$ formed from [dimethylamino-^{14}C]aminopyrine in nitrous oxide-treated rats. Hepatology 1984;4:871–6.
10. Deacon R, Perry J, Lumb M, Chanarin I. Increased urinary excretion of formiminoglutamic acid in nitrous oxide-treated rats and its reduction by methionine. Eur J Biochem 1983;129: 627–8.
11. Blundell E, Matthews JH, Allen SM, Middleton AM, Morris JE, Wickramasinghe SN. Importance of low serum vitamin B_{12} and red cell folate concentrations in elderly hospital inpatients. J Clin Pathol 1985;38:1179–84.
12. Matthews JH, Clark DM, Abrahamson GM. Effect of therapy with vitamin B_{12} and folic acid on elderly patients with low concentrations of serum vitamin B_{12} or erythrocyte folate but normal blood counts. Acta Haematol 1988;79:84–7.
13. Logan RF, Elwis A, Forrest MJ, Lawrence ACK. Mechanisms of vitamin B_{12} deficiency in elderly inpatients. Age Ageing 1989;18:4–10.
14. Grady S, Osterloh J. Improved enzymic assay for serum formate with colorimetric end-point. J Anal Toxicol 1986;10: 1–5.
15. Shane B, Stokstad ELR. Folates in the synthesis and catabolism of histidine. In: Blakley RL, Benkovic SJ, eds. Folates and pterins. Volume 1. Chemistry and biochemistry of folates. New York: John Wiley & Sons, 1984:433–55.
16. Koblin DD, Watson JE, Deady JE, Stokstad ELR, Eger EI II. Inactivation of methionine synthetase by nitrous oxide in mice. Anesthesiology 1981;54:318–24.
17. Koblin DD, Tomerson BW. Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice. Br J Anaesth 1990;64:214–23.
18. Johlin FC, Fortman CS, Nghiem DD, Tephly TR. Studies on the role of folic acid and folate-dependent enzymes in human methanol poisoning. Mol Pharmacol 1987;31:557–61.
19. Hawkins RA, Snider MT, Russell GB, Davis DW, Biebuyck JF. Does nitrous oxide inactivation of methione synthase decrease folic acid activity in man? Anesthesiology 1987;67:A292.
20. Herbert V. Making sense of laboratory tests of folate status: folate requirements to sustain normality. Am J Hematol 1987; 26:199–207.
21. Rosenberg IH, Bowman BB, Cooper BA, Halsted CH, Lindenbaum J. Folate nutrition in the elderly. Am J Clin Nutr 1982;36:1060–6.
22. Lumb M, Perry J, Deacon R, Chanarin I. Changes in plasma folate levels in rats inhaling nitrous oxide. Scand J Haematol 1981;26:61–4.
23. Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. Br J Haematol 1983;53:189–200.
24. Lumb M, Perry J, Deacon R, Chanarin I. Urinary folate loss following inactivation of vitamin B_{12} by nitrous oxide in rats. Br J Haematol 1982;51:235–42.
25. Gokben M, Esener Z. Effect of nitrous oxide on serum vitamin-B_{12} levels under surgical anesthesia. Acta Anaesthesiol Belg 1985;36:71–7.

26. Muir M, Chanarin I. Conversion of endogenous cobalamins into microbiologically-inactive cobalamin analogues in rats by exposure to nitrous oxide. Br J Haematol 1984;58:517–23.
27. Lampe GH, Wauk LZ, Donegan JH, et al. Effect on outcome of prolonged exposure of patients to nitrous oxide. Anesth Analg 1990;71:586–90.
28. Waldman FM, Koblin DD, Lampe GH, Wauk LZ, Eger EI II. Hematologic effects of nitrous oxide in surgical patients. Anesth Analg 1990;71:618–24.
29. Eger EI II, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85.

Hematologic Effects of Nitrous Oxide in Surgical Patients

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WALDMAN FM, KOBLIN DD, LAMPE GH, WAUK LZ, EGER EI II. Hematologic effects of nitrous oxide in surgical patients. Anesth Analg 1990;71:618–24.

Nitrous oxide can cause hematologic abnormalities, including death, if it is administered for several days. However, the adverse hematologic effects of its use for surgical anesthesia are unclear. Accordingly, we have studied the hematologic responses of patients undergoing procedures involving hematologic stress or prolonged anesthesia with and without nitrous oxide. We measured red cell count, hemoglobin concentration, mean red cell volume, reticulocyte count, platelet count, mean platelet volume, blood leukocyte level, and leukocyte differential in patients undergoing total hip arthroplasty or removal of an acoustic neuroma. Nitrous oxide did not affect the production of red blood cells or platelets. Nitrous oxide treatment was associated with an increase in postoperative leukocyte levels that was modestly but significantly smaller than that found in patients not given nitrous oxide. There was no evidence that this small decrease in maximal leukocytosis adversely affected clinical outcome.

Key Words: ANESTHETICS, GASES—nitrous oxide. BLOOD—hematologic responses to nitrous oxide.

Nitrous oxide (N_2O) inactivates the vitamin B_{12} moiety of the enzyme methionine synthase (1,2). This inactivation disrupts biosynthetic pathways active in folate metabolism, impairs DNA synthesis, and can induce bone marrow depression like that associated with B_{12} deficiency.

Lassen et al. first described the hematologic toxicity of prolonged N_2O administration in patients being treated for tetanus (3). Others have confirmed such toxicity (4–8) and demonstrated N_2O-induced megaloblastic bone marrow failure with peripheral cytopenia. Bone marrow cells exposed to N_2O exhibit an abnormal response to the deoxyuridine suppression test, reflecting an impaired pathway for de novo thymidine synthesis due to inactivation of methionine synthase (7,9–13).

Although administration of N_2O for several days produces untoward hematologic changes, only two anecdotal reports suggest such adverse effects in surgical patients undergoing anesthesia for more usual periods of time (14,15). Accordingly, we have measured the changes in peripheral blood cells in patients undergoing procedures involving hematologic stress and prolonged anesthesia with and without N_2O.

Materials and Methods

Twenty-three patients scheduled for elective total hip arthroplasty (orthopedic patients) and 26 patients scheduled for resection of an acoustic neuroma (neurosurgical patients) consented to participate in our institutionally approved study. All patients received isoflurane, thiopental, and vecuronium, but were randomly assigned to receive 50%–70% N_2O or 100% oxygen (O_2). In addition, orthopedic patients received spinal (tetracaine) or epidural (lidocaine) anesthesia. Premedication (triazolam and/or morphine or none) and the intraoperative use of fentanyl and edrophonium/atropine were controlled by the attending anesthesiologist, not by study protocol. Inhaled isoflurane concentrations and doses of tetracaine and lidocaine used were adjusted to maintain appropriate levels of anesthesia.

Preoperatively, we measured levels of serum vitamin B_{12}, serum folate, and red blood cell (RBC) folate using standard radioassays (CIBA Corning Diagnostics). Preoperative peripheral venous blood samples were drawn in the operating room or up to 1 day

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Supported by NIA PO1 AG3104 and the Anesthesia Research Foundation.

Received from the Departments of Laboratory Medicine and Anesthesia, University of California, San Francisco, San Francisco, California. Accepted for publication July 3, 1990.

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Table 1. Patient Demographics

	Orthopedic		Neurosurgical	
	N_2O	O_2	N_2O	O_2
n	12	11	13	13
Age (yr)	66 ± 12.5	64 ± 9.3	49.7 ± 10.8	47.6 ± 10.2
Sex (% male)	25	50	77	62
Duration of anesthesia (h)	3.0 ± 0.8	3.6 ± 1.2	9.3 ± 2.4	9.9 ± 3.8
Serum B_{12} (pg/mL)	472 ± 320	421 ± 168	568 ± 226	518 ± 148
Serum folate (ng/mL)	9.6 ± 3.4	10.5 ± 4.2	7.6 ± 4.0	6.4 ± 2.5
RBC folate (ng/mL)	190 ± 87	192 ± 79	126 ± 40	144 ± 41
Blood loss (mL)	1612 ± 594	1740 ± 866	448 ± 184	456 ± 321
Autotransfusions (U/patient)	1.1	1.9	0	0.3
Other transfusions (U/patient)	0.4	0.6	0	0.1

N_2O, nitrous oxide; O_2, oxygen; RBC, red blood cell.
Except for number (n), sex, autotransfusions, and other transfusions, values are expressed as mean ± SD.

before surgery. When possible, postoperative samples were drawn at days 1, 2, 3, 6, 9, and 11 after surgery for orthopedic patients and on days 1, 2, 3, 4, and 5 for neurosurgical patients. Preoperative and postoperative measurements of peripheral blood hemoglobin (Hb, g/dL), RBC count ($10^6/\mu L$), mean red cell volume (fL), red cell distribution width (%, the coefficient of variation of the red cell volume measurement), platelet count ($10^3/\mu L$), mean platelet volume (fL), absolute white blood cell (WBC) count, ($10^3/\mu L$), and white cell differential (absolute values, $10^3/\mu L$) were made by an automated counter (H1, Technicon Instruments, Tarrytown, N.Y.). Reticulocyte counts ($10^3/\mu L$) were obtained by staining blood samples with thioflavin T or ethidium bromide; the count obtained with each technique was calibrated with appropriate controls to maintain equivalent results. Cells were analyzed by flow cytometry because this technique measures the RNA content of 10,000 red cells and is more reliable and accurate than previously used manual methods (16,17). Hypersegmentation of neutrophils was measured both as mean lobes per nucleus in 200 neutrophils and as a percentage of neutrophils having five or more lobes (lobes must be separated from each other by a thin filament).

We compared hematologic values obtained during anesthesia with and without N_2O within and between the two surgical groups using Student's *t*-tests. We calculated absolute hematologic values, absolute changes from baseline, and the proportional change from baseline for each day of study. Data from one patient who had a preoperative WBC count of $19{,}000/\mu L$ were excluded from the analyses of white count and neutrophils.

Results

Age and sex did not differ between patients given N_2O or O_2 for either orthopedic or neurosurgical groups (Table 1). Orthopedic patients were older than neurosurgical patients, and the duration of anesthesia was appreciably shorter for orthopedic patients.

Preoperative levels of serum B_{12}, serum folate, and RBC folate did not differ between the two anesthetic groups. However, orthopedic and neurosurgical groups differed, orthopedic patients having significantly higher RBC folate and serum folate levels ($P < 0.006$) preoperatively, with a trend toward higher serum B_{12} in neurosurgical patients ($P = 0.156$). Low RBC folate levels (<130 ng/mL) occurred in 4 of 23 orthopedic patients, but in 15 of 26 neurosurgical patients.

The two anesthetic groups did not differ in intraoperative or postoperative blood loss and transfusion requirement (Table 1). However, orthopedic patients lost more blood (1670 mL) than neurosurgical patients (452 mL, $P < 0.0001$) and had greater transfusion requirements (2.0 U vs 0.2 U per patient). Orthopedic patients had routinely donated 2–3 autologous units in the 6 wk preceding surgery, and 82% of transfused units were autologous.

Postoperatively, RBC counts initially decreased (Tables 2 and 3, Figure 1), then returned toward preoperative levels, with no difference between anesthetic groups. Blood Hb concentration paralleled RBC count, with decreases on days 1 and 2, then a return toward baseline, with no detectable effect of N_2O. Preoperatively, RBC and Hb values were below normal for orthopedic patients due to recent donations (Hb normal range: women—12–16 g/dL, men—

Table 2. Hematologic Values in Orthopedic Patients

	Postoperative day						
Variable	0	1	2	3	6	9	11
RBC count							
O_2	*n* = 11	*n* = 10	*n* = 10	*n* = 11	*n* = 10	*n* = 9	*n* = 9
	3.66 ± 0.14	3.28 ± 0.12	3.21 ± 0.14	3.42 ± 0.15	3.56 ± 0.14	3.59 ± 0.17	3.55 ± 0.17
N_2O	*n* = 12	*n* = 12	*n* = 12	*n* = 12	*n* = 11	*n* = 10	*n* = 8
	3.60 ± 0.12	3.36 ± 0.09	3.32 ± 0.10	3.37 ± 0.10	3.39 ± 0.13	3.77 ± 0.16	3.58 ± 0.13
Hb							
O_2	*n* = 11	*n* = 10	*n* = 10	*n* = 11	*n* = 10	*n* = 9	n = 9
	11.6 ± 0.4	10.4 ± 0.3	10.3 ± 0.5	10.9 ± 0.5	11.3 ± 0.4	11.3 ± 0.5	11.1 ± 0.5
N_2O	*n* = 12	*n* = 12	*n* = 12	*n* = 12	*n* = 11	*n* = 10	*n* = 8
	11.3 ± 0.4	10.3 ± 0.3	10.4 ± 0.4	10.4 ± 0.4	10.4 ± 0.5	11.5 ± 0.5	10.9 ± 0.5
MCV							
O_2	*n* = 11	*n* = 10	*n* = 10	*n* = 11	*n* = 10	*n* = 9	*n* = 9
	93.8 ± 1.4	94.2 ± 1.5	93.9 ± 1.6	93.8 ± 1.4	94.2 ± 1.5	93.7 ± 1.0	94.3 ± 1.1
N_2O	*n* ± 12	*n* = 12	*n* = 12	*n* = 12	*n* = 11	*n* = 10	*n* = 8
	92.6 ± 1.4	92.3 ± 1.3	92.2 ± 1.2	91.9 ± 1.5	94.2 ± 1.3	91.5 ± 1.0	92.6 ± 0.9
Reticulocytes							
O_2	*n* = 10	*n* = 10	*n* = 9	*n* = 10	*n* = 10	*n* = 7	*n* = 8
	91 ± 15	94 ± 13	81 ± 10	99 ± 10	118 ± 20	95 ± 10	100 ± 12
N_2O	*n* = 10	*n* = 11	*n* = 10	*n* = 11	*n* = 11	*n* = 8	*n* = 8
	73 ± 8	80 ± 10	81 ± 8	89 ± 8	84 ± 11	102 ± 10	98 ± 18
Platelets							
O_2	*n* = 11	*n* = 10	*n* = 10	*n* = 11	*n* = 10	*n* = 9	*n* = 9
	287 ± 19	245 ± 16	226 ± 15	239 ± 15	369 ± 24	494 ± 47	576 ± 59
N_2O	*n* = 12	*n* = 12	*n* = 12	*n* = 12	*n* = 11	*n* = 10	*n* = 8
	263 ± 25	206 ± 16	195 ± 17	209 ± 15	342 ± 20	473 ± 40	489 ± 40
WBC count							
O_2	*n* = 11	*n* = 10	*n* = 10	*n* = 11	*n* = 10	*n* = 9	*n* = 9
	5.2 ± 0.4	9.0 ± 0.8	9.7 ± 0.7	9.2 ± 0.7	7.9 ± 0.3	7.9 ± 0.5	8.5 ± 0.5
N_2O	*n* = 12	*n* = 12	*n* = 12	*n* = 12	*n* = 11	*n* = 10	*n* = 8
	6.0 ± 0.8	8.8 ± 0.8	8.8 ± 0.8	8.2 ± 0.9	7.7 ± 1.1	7.6 ± 0.8	7.4 ± 0.8
Neutrophils							
O_2	*n* = 11	*n* = 10	*n* = 9	*n* = 10	*n* = 10	*n* = 8	*n* = 9
	3.1 ± 0.3	7.1 ± 0.7	7.4 ± 0.7	7.3 ± 0.5	5.1 ± 0.4	5.0 ± 0.5	6.0 ± 0.5
N_2O	*n* = 12	*n* = 11	*n* = 12	*n* = 11	*n* = 11	*n* = 9	*n* = 8
	3.4 ± 0.5	6.8 ± 0.7	6.9 ± 0.6	6.2 ± 0.8	5.1 ± 0.9	4.8 ± 0.8	4.8 ± 0.7
Neut seg							
O_2	*n* = 10			*n* = 10	*n* = 7	*n* = 5	
	1.87 ± 0.10			1.73 ± 0.07	1.62 ± 0.11	1.76 ± 0.04	
N_2O	*n* = 12			*n* = 11	*n* = 10	*n* = 9	
	1.94 ± 0.09			1.74 ± 0.05	1.73 ± 0.08	1.82 ± 0.07	

RBC, red blood cell; O_2, oxygen; N_2O, nitrous oxide; Hb, hemoglobin; MCV, mean red cell volume; WBC, white blood cell; Neut seg, mean neutrophil lobe count.

Values are mean ± SEM.

13.5–17.5 g/dL; RBC normal range: women—4–5.2 × 10^6/mm^3, men—4.2–5.6 × 10^6/mm^3).

Mean red cell volume and red cell distribution width showed no consistent effect of N_2O and no trends during the postoperative course. The reticulocyte count increased postoperatively in most patients, with no discernable effect of N_2O; however, the large variability in reticulocyte count may have masked any effect.

Platelet count decreased on postoperative days 1–3 in orthopedic patients, followed by rebound thrombocytosis to levels approximately twice baseline on days 6, 9, and 11 (Figure 2). No effect of N_2O was observed in either orthopedic or neurosurgical patients.

The effect of N_2O on WBC production was measured by leukocyte number and by neutrophil segmentation. In orthopedic patients, WBC count increased on the first postoperative day, then decreased gradually during the rest of their hospital stay (Figure 3). Orthopedic patients given N_2O had a smaller proportional increase in WBC count than those given O_2. This difference between anesthetic groups was most significant on day 2 ($P = 0.06$) and

Table 3. Hematologic Values in Neurosurgical Patients

		Postoperative day			
Variable	Preoperative	1	2	3	5
RBC count					
O_2	$n = 12$	$n = 13$	$n = 9$	$n = 7$	$n = 9$
	4.20 ± 0.11	3.87 ± 0.12	3.78 ± 0.15	3.79 ± 0.19	3.98 ± 0.16
N_2O	$n = 13$	$n = 12$	$n = 8$	$n = 9$	$n = 7$
	4.54 ± 0.17	4.24 ± 0.21	3.87 ± 0.20	4.11 ± 0.26	4.57 ± 0.35
Hb					
O_2	$n = 12$	$n = 12$	$n = 8$	$n = 7$	$n = 9$
	12.9 ± 0.3	11.9 ± 0.4	11.6 ± 0.6	11.9 ± 0.7	12.0 ± 0.4
N_2O	$n = 13$	$n = 12$	$n = 8$	$n = 9$	$n = 7$
	14.1 ± 0.4	13.2 ± 0.5	12.1 ± 0.5	12.6 ± 0.6	13.8 ± 0.8
MCV					
O_2	$n = 12$	$n = 13$	$n = 9$	$n = 7$	$n = 9$
	90.0 ± 1.8	89.8 ± 1.6	88.3 ± 1.3	90.9 ± 2.0	88.4 ± 1.9
N_2O	$n = 13$	$n = 12$	$n = 8$	$n = 9$	$n = 7$
	90.6 ± 1.8	90.5 ± 1.8	93.3 ± 2.0	90.9 ± 2.2	87.4 ± 2.7
Reticulocytes					
O_2	$n = 12$				$n = 9$
	127 ± 11				136 ± 5
N_2O	$n = 13$				$n = 12$
	102 ± 11				95 ± 9
Platelets					
O_2	$n = 12$				$n = 9$
	280 ± 13				301 ± 28
N_2O	$n = 13$				$n = 8$
	316 ± 37				365 ± 42
WBC count					
O_2	$n = 11$	$n = 12$	$n = 8$	$n = 6$	$n = 8$
	6.0 ± 0.5	14.7 ± 1.1	14.3 ± 1.5	14.4 ± 3.1	9.2 ± 0.7
N_2O	$n = 13$	$n = 12$	$n = 8$	$n = 9$	$n = 7$
	6.3 ± 0.5	13.6 ± 0.8	13.0 ± 1.1	10.4 ± 0.8	8.1 ± 0.3
Neutrophils					
O_2	$n = 11$				$n = 8$
	3.8 ± 0.5				6.5 ± 0.6
N_2O	$n = 13$				$n = 7$
	4.0 ± 0.4				5.3 ± 0.2
Neut seg					
O_2	$n = 10$				$n = 10$
	2.10 ± 0.09				2.0 ± 0.07
N_2O	$n = 8$				$n = 8$
	1.96 ± 0.07				1.93 ± 0.08

RBC, red blood cell; O_2, oxygen; N_2O, nitrous oxide; Hb, hemoglobin; MCV, mean red cell volume; WBC, white blood cell; Neut seg, mean neutrophil lobe count.

Values are mean ± SEM.

day 3 ($P = 0.02$). Increases in neutrophil number accounted for most of the increase in WBC count (Figure 4); the greatest difference between orthopedic patients given N_2O versus those given O_2 alone was seen on day 3 ($P = 0.05$). Neurosurgical patients had a similar pattern of increased WBC and neutrophil counts immediately after surgery, followed by a decrease toward baseline values (Figure 3). Again, patients given N_2O had smaller proportional increases than those given O_2 alone, but this difference was not significant on any given day.

The presence of hypersegmented neutrophils in peripheral blood is pathognomonic of B_{12} deficiency and is due to abnormal DNA synthesis associated with altered methionine synthase activity. There was no evidence of increased numbers of hypersegmented neutrophils having five or more lobes in any group. Values for the two anesthetic groups did not differ. The two anesthetic groups also did not differ in average lobe count per cell (Tables 2 and 3). In fact, lobe counts tended to decrease immediately postoperatively, perhaps due to a slight left shift in neutrophil maturity associated with the increase in neutrophil number.

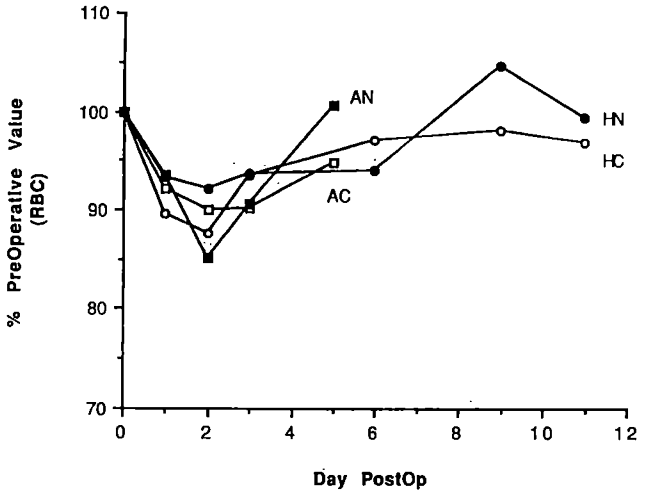

Figure 1. Change in RBC count after surgery as a proportion of the preoperative (day 0) value. AC, acoustic neuroma controls; AN, acoustic neuroma patients given N_2O; HC, hip surgery controls; HN, hip surgery patients given N_2O.

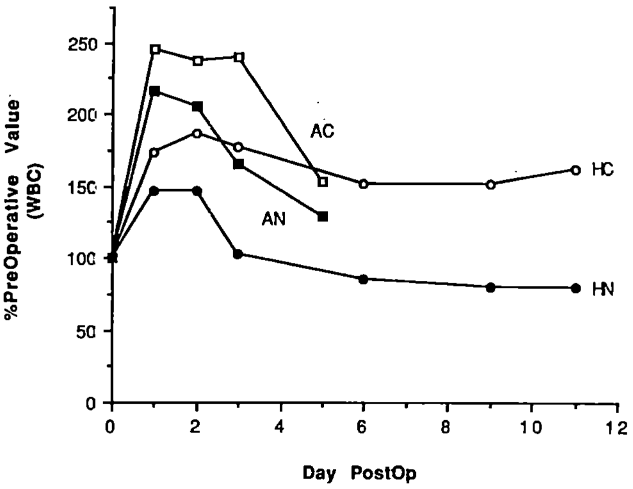

Figure 3. Change in WBC count after surgery as a proportion of the preoperative (day 0) value. AC, acoustic neuroma controls; AN, acoustic neuroma patients given N_2O; HC, hip surgery controls; HN, hip surgery patients given N_2O.

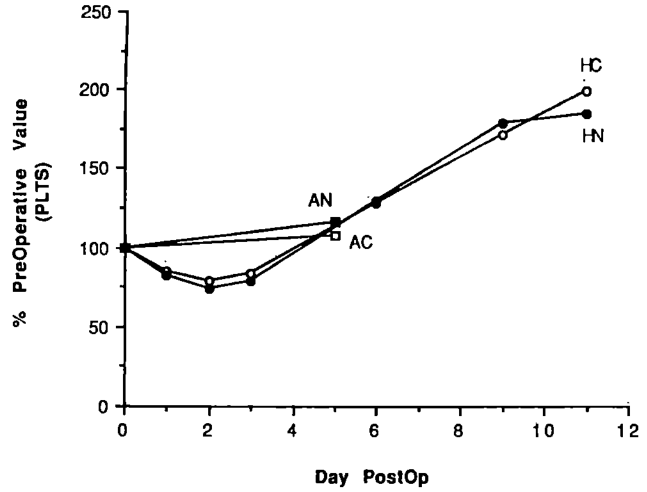

Figure 2. Change in platelet count after surgery as a proportion of the preoperative (day 0) value. AC, acoustic controls; AN, acoustic patients given N_2O; HC, hip surgery controls; HN, hip surgery patients given N_2O.

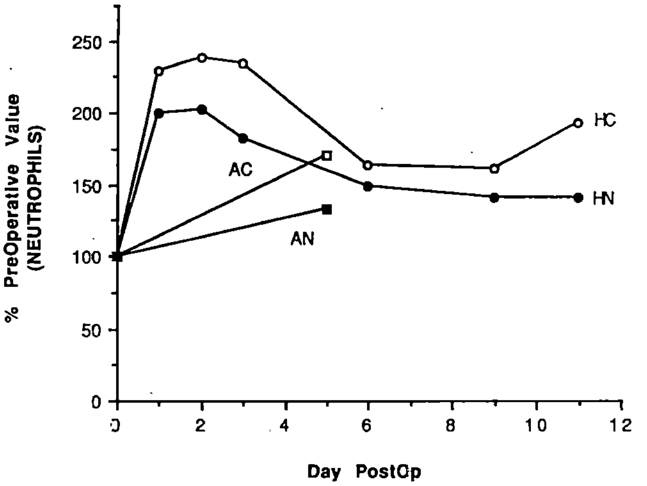

Figure 4. Change in neutrophil count after surgery as a proportion of the preoperative (day 0) value. AC, acoustic neuroma controls; AN, acoustic neuroma patients given N_2O; HC, hip surgery controls; HN, hip surgery patients given N_2O.

Discussion

Despite the known effect of N_2O on DNA synthesis mediated by methionine synthase (7,9), despite the hematopoietic stress imposed by blood loss in orthopedic patients, and despite the prolonged 9-h exposure to N_2O in neurosurgical patients, measures of red cell mass (RBC, Hb, mean red cell volume, red cell distribution width, and reticulocytes) were not affected by the use of N_2O. Absence of an effect may be just that: even the "prolonged" exposure in our patients (9 h) may be insufficient to impair hematopoiesis. Alternatively, a subtle impairment may have occurred but been masked by other factors such as the variability caused by blood loss and transfusion. Additionally, our measures of hematopoiesis may have been too insensitive to reveal shifts in red cell production capacity. Mean measures of the entire red cell population (mean red cell volume, red cell distribution width) may not be sensitive to small shifts in production unless effects are chronic in nature.

In orthopedic patients, reticulocyte counts may not have reflected the patient's postoperative production capacity because (a) most patients were stimulated to produce reticulocytes preoperatively by blood donation; and (b) patients were then given autologous blood transfusions that had variable reticulocyte content. Neurosurgical patients were not subjected to appreciable blood loss, so that their capacity for production of reticulocytes was not challenged.

Postoperatively, platelet number initially decreased. There followed a rebound thrombocytosis, the expected response of the bone marrow to blood loss or thrombocytopenia (18). Administration of N_2O did not affect this response. The lack of effect of N_2O might be due to the large reserve of potential platelets residing in existing megakaryocytes. That is, the production of platelets might not require DNA synthesis.

Total WBC counts (and total neutrophils) increased postoperatively in both orthopedic and neurosurgical patients. Orthopedic patients given N_2O had a smaller leukocyte increment than those given O_2. A similar but not statistically significant trend was seen in neurosurgical patients. Neutrophil segmentation was not affected by the use of N_2O. Impaired neutrophil production mediated by inactivation of methionine synthase should not be apparent until 2–3 days after surgery (the minimal time for blasts/promyelocytes to mature and be released to the periphery), yet leukocyte levels increased within the first 2 postoperative days. Therefore, the effect of N_2O on the neutrophilic response, if any, is probably due to an effect on hormonal mediators of stress rather than on DNA synthesis. Even if that is so, N_2O did not limit neutrophil production within 24–48 h of surgery.

The slightly smaller rise in leukocytes in patients given N_2O might reflect a decreased capacity to meet the stress of infection. However, the difference, albeit statistically significant, was small, and was not associated with an increased incidence of infection in patients given N_2O. We do not believe that the decrease in leukocyte levels associated with N_2O significantly affected the clinical outcomes of our patients. The absence of a clinically relevant effect is supported by similar findings in additional studies of the effects of N_2O on organ function and folate and vitamin B_{12} metabolism (19–22). It also is suggested by a comparison of the clinical outcomes of our two surgical groups. If a difference due to N_2O is mediated through an effect on leukocytosis, one might expect a trend toward an increased incidence in untoward outcomes in neurosurgical patients given N_2O because the duration of anesthesia in these patients was three times that in patients undergoing orthopedic replacement. No such increase in untoward outcomes was found.

One may argue that N_2O may be harmful to a particular subset of patients, such as those with severe B_{12} or folate deficiency (15). However, our population included elderly patients and patients with low RBC folate levels (especially in the neurosurgical group). Absence of an appreciable effect on hematologic variables in these patients after 9 or more hours of an anesthetic including N_2O suggests that this agent should not present a problem, even in patients having a mild folate (or B_{12}) deficiency. It also suggests that N_2O may be included in the anesthetic regimen of most surgical patients without compromising postoperative hematologic function. However, we cannot exclude the possibility that severe B_{12} or folate deficiency might predispose patients to adverse sequelae with administration of N_2O.

We gratefully acknowledge the assistance with study design and statistical analysis provided by Dr. David Heilbron and Mark Spitalny. We also thank Dr. Laurence Corash and Winifred von Ehrenberg for reviewing the manuscript.

References

1. Shane B, Stokstad E. Vitamin B12-folate interrelationships. Ann Rev Nutr 1985;5:115–41.
2. Banks RGS, Henderson RJ, Pratt JM. Reactions of gases in solution. III. Some reactions of nitrous oxide with transition-metal complexes. J Chem Soc Sec A 1968;3:2886–90.
3. Lassen HCA, Henriksen E, Neukirch F, Kristensen HS. Treatment of tetanus. Severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. Lancet 1956;i:527–30.
4. Nunn JF, Sharer NM, Gorchein A, Jones JA, Wickramasinghe SN. Megaloblastic haemopoiesis after multiple short-term exposure to nitrous oxide. Lancet 1982;i:1379–81.
5. Chanarin I. Cobalamins and nitrous oxide: a review. J Clin Pathol 1980;33:909–16.
6. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. Br J Anaesth 1987;59:3–13.
7. O'Sullivan H, Jennings F, Ward K, McCann S, Scott JM, Weir DG. Human bone marrow biochemical function and megaloblastic hematopoiesis after nitrous oxide anesthesia. Anesthesiology 1981;55:645–9.
8. Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. Br J Haematol 1983;53:7–8.
9. Amess JAL, Burman JF, Rees GM, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 1978;ii:339–40.
10. Amos RJ, Amess JA, Hinds CJ, Mollin DL. Investigations into the effect of nitrous oxide anaesthesia on folate metabolism in patients receiving intensive care. Chemioterapia 1985;4:393–9.
11. Das KC, Manusselis C, Herbert V. In vitro DNA synthesis by bone marrow cells and PHA-stimulated lymphocytes. Br J Haematol 1980;44:51–63.
12. Kano Y, Sakamoto S, Sakuraya K, et al. Effects of leucovorin and methylcobalamin with N_2O anesthesia. J Lab Clin Med 1984;104:711–7.
13. Skacel PO, Chanarin I, Hewlett A, Nunn JF. Failure to correct nitrous oxide toxicity with folinic acid (letter). Anesthesiology 1982;57:557–8.

14. Berger JJ, Modell JH, Sypert GW. Megaloblastic anemia and brief exposure to nitrous oxide—a causal relationship (letter). Anesth Analg 1988;67:197–8.
15. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B12-deficient subjects? JAMA 1986;255:1605–6.
16. Corash L, Rheinschmidt M, Lieu S, Meers P, Brew E. Enumeration of reticulocytes using fluorescence-activated flow cytometry. Pathol Immunopathol Res 1988;7:381–94.
17. Savage RA, Skoog DP, Rabinovitch A. Analytic inaccuracy and imprecision in reticulocyte counting: a preliminary report from the College of American Pathologists' reticulocyte project. Blood Cells 1985;11:97–112.
18. Levin J, Bessman JD. The inverse relation between platelet volume and platelet number. J Lab Clin Med 1983;101:295–307.
19. Koblin DD, Tomerson MS, Waldman FM, Lampe GH, Wauk LZ, Eger EI II. Effect of nitrous oxide on folate and vitamin B_{12} metabclism in patients. Anesth Analg 1990;71:610–7.
20. Eger EI II, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg 1990;71:575–85.
21. Lampe GH, Wauk LZ, Whitendale P, et al. Postoperative hypoxemia after nonabdominal surgery: a frequent event not caused by nitrous oxide. Anesth Analg 1990;71:597–601.
22. Lampe GH, Wauk LZ, Whitendale P, Way WL, Murray W, Eger EI II. Nitrous oxide does not impair hepatic function in young or old surgical patients. Anesth Analg 1990;71:606–9.

Thoracic Epidural Anesthesia Improves Global and Regional Left Ventricular Function During Stress-Induced Myocardial Ischemia in Patients With Coronary Artery Disease

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KOCK M, BLOMBERG S, EMANUELSSON H, LOMSKY M, STRÖMBLAD S-O, RICKSTEN S-E. Thoracic epidural anesthesia improves global and regional left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease. Anesth Analg 1990;71:625–30.

The aim of the present investigation was to study the effects of high thoracic epidural anesthesia (TEA), including the cardiac sympathetic segments, on ischemic ST-segment changes and left ventricular global and regional wall motion abnormalities. Ten patients with a two- or three-vessel coronary artery disease, all treated with the β-adrenergic blocker metoprolol because of severe stable angina pectoris, performed two identical exercise stress tests, the first without TEA (control exercise) and the second with TEA (TEA exercise). Before each stress test, intravenous metoprolol was given to achieve maximal or near maximal β-adrenoceptor blockade. Systolic and diastolic arterial pressures (radial artery cannula), heart rate, and rate-pressure product, as well as global and regional ejection fractions, using equilibrium radionuclide angiography in the left anterior oblique projection, were measured at rest and during maximal exercise. ST-segment analysis (V_3 or V_5) was performed, and the regional wall motion score was calculated at control exercise and TEA exercise. Intravenous metoprolol or intravenous metoprolol plus TEA at rest did not cause any significant changes of any of the variables. During TEA exercise, systolic arterial pressure, diastolic arterial pressure, and rate-pressure product, but not heart rate, were significantly lower compared to control exercise. The global and anterolateral ejection fractions were significantly higher (52.8% versus 46.5% and 53.2% versus 46.0%, respectively, $P < 0.05$), and the regional wall motion score was significantly lower (8.8 versus 11.8, $P < 0.01$) during TEA exercise than during control exercise. ST-segment depression was significantly lower during TEA exercise (−1.03 versus −1.84 mV, $P < 0.01$). It is concluded that cardiac sympathetic blockade with TEA, in patients with coronary artery disease, improves ischemia-induced left ventricular global and regional wall motion abnormalities at a certain physical stress, associated with less pronounced ST-segment depression.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—myocardial function. HEART, ISCHEMIA—thoracic epidural anesthesia.

During myocardial ischemia cardiac sympathetic afferents are activated, which is essential for the perception of cardiac pain (1). Thoracic epidural anesthesia (TEA), with a selective blockade of cardiac sympathetic segments, has been shown to be effective in the treatment of severe chest pain in patients with myocardial infarction (2,3). Recently, it was demonstrated that TEA effectively controls pain also in patients with unstable angina pectoris and chest pain at rest in spite of maximal pharmacologic treatment, including nitroglycerin infusion (4). Furthermore, it has been reported that during anginal pain, TEA induces a decrease in systolic arterial pressure, heart rate, and left ventricular filling pressure, whereas coronary perfusion pressure is maintained (5). Thus, during ischemic chest pain at rest, TEA reduces the major determinants of myocardial oxygen demand, associated with an attenuation of ischemic ST-T segment changes in some patients. In addition, it was shown that during myocardial ischemia, TEA may, if anything, improve left ventricular

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Supported by grants from the Swedish Medical Research Council (No. 08682), the Swedish Association for Heart and Lung Diseases, Laerdal's Foundation, and Tore Nilsson's Foundation.

Received from the Department of Anesthesia and Intensive Care and the Department of Internal Medicine I, Section of Cardiology, University of Gothenburg, Sahlgren's Hospital, Gothenburg, Sweden. Accepted for publication August 3, 1990.

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Table 1. Clinical Data and Angiographic Findings

Patient	Sex	Age (yr)	MI	Number of obstructed vessels	Main stem arterial stenosis	β-Adrenergic blockers	Calcium channel blockers	Long-acting nitrates
1	F	51	1	3	–	+	+	+
2	F	51	0	3	–	+	+	+
3	M	72	2	3	–	+	–	+
4	M	55	0	2	–	+	+	+
5	M	47	0	2	–	+	–	+
6	M	59	2	3	–	+	–	–
7	F	73	1	3	+	+	–	+
8	F	53	1	3	+	+	–	+
9	M	67	1	3	–	+	–	+
10	M	53	0	2	–	+	+	+

MI, myocardial infarction.

performance as the TEA-induced decrease in left ventricular filling pressure was accompanied by an unchanged stroke volume (5).

The aim of the present investigation was to study in more detail the effects of cardiac sympathectomy by TEA on left ventricular function during myocardial ischemia. Patients with stable angina pectoris due to documented coronary artery disease performed two identical exercise stress tests in the supine position, one with and one without TEA. Ischemia-induced changes in left ventricular global and regional wall motion abnormalities were studied using equilibrium radionuclide angiocardiography.

Materials and Methods

This study was approved by the Human Ethics Committee of the University of Gothenburg. Patients undergoing routine coronary angiography because of severe but stable angina pectoris were, after informed consent, included if they (a) were maintained on treatment with β-blockers, and (b) had ST-segment depression ≥1 mV on anterolateral leads (V_3, V_5) during a standardized exercise stress test. Ten patients participated in the study, and their individual data, including cardiac history, angiographic findings, and cardiac medication, are shown in Table 1. The mean age of the patients was 58 ± 3 yr (range, 47–73 yr). Five patients had previous myocardial infarction(s). All patients had a two- or three-vessel coronary artery disease, and occlusion of the left main stem artery was seen in two patients.

Thoracic Epidural Anesthesia

The thoracic epidural catheter was inserted the day before the experimental procedure. The catheter was inserted through one of the third to fifth thoracic vertebral interspaces, employing a median approach and the loss of resistance technique. The aim was to place the tip of the catheter at the T_1-T_2 level. After an initial test dose of 2 mL, incremental doses of 1–2 mL of bupivacaine (5 mg/mL) were injected every 10 min to induce a blockade of, at the least, cardiac sympathetic segments T_{1-5}. The extent of blockade was evaluated 20–30 min after the last injection by measuring the extent of loss of temperature discrimination ability. The individually titrated amounts of epidural bupivacaine were given on the experimental day.

Equilibrium Radionuclide Angiocardiography

Patients' own red blood cells were labeled with 925 MBq of technetium 99m using standard in vivo-in vitro labeling techniques. Imaging was performed with a small field of view single-crystal gamma camera in the left anterior oblique position that best separated the right and left ventricles and with 20° caudal tilt. The gamma camera was interfaced to a computer system. Studies were done with the patients in the supine position. Data were collected in frame mode using 32 frames per R-R interval with the gate tolerance ±10% of the cardiac cycle. The computer rejected premature beats and the following beats. The acquisition was stopped when the left ventricular region of interest contained approximately 150 counts/pixel.

The left ventricular time-activity curve was generated using a semiautomated edge-detection algorithm with varying region of interest. Ejection fraction and peak filling rate were calculated from left ventricular time-activity curve after background subtraction and filtering by a Fourier amplitude and phase fit that retained only the first six harmonics of

Table 2. Effects of Metoprolol and Metoprolol Plus Thoracic Epidural Anesthesia on Hemodynamics and Global and Regional Left Ventricular Function at Rest

	SAP (mm Hg)	DAP (mm Hg)	HR (beats/min)	RPP (beats/min × mm Hg × 10^3)	GEF (%)	REF_1 (%)	REF_2 (%)	REF_3 (%)
Control	147 ± 7	67 ± 3	59 ± 3	8.6 ± 0.4	58.1 ± 3.3	60.6 ± 5.9	53.2 ± 5.8	49.6 ± 3.7
Metoprolol	148 ± 8	71 ± 5	58 ± 2	8.5 ± 0.5	56.9 ± 3.7	60.0 ± 5.9	52.9 ± 5.5	47.1 ± 2.7
Metoprolol + TEA	134 ± 9	68 ± 3	59 ± 2	7.9 ± 0.6	56.8 ± 3.0	60.6 ± 5.2	53.5 ± 5.9	46.2 ± 3.1

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; RPP, rate-pressure product; GEF, global ejection fraction; REF_1, anterolateral regional ejection fraction; REF_2, apicoposterior regional ejection fraction; REF_3, anteroseptal regional ejection fraction; TEA, thoracic epidural anesthesia.

the curve. The fourth, fifth, and sixth harmonics were multiplied by 0.75, 0.5, and 0.25, respectively. Global left ventricular ejection fraction (GEF) was calculated by subtracting end-systolic from end-diastolic counts and dividing by end-diastolic counts.

Regional Ejection Fraction

The left ventricle was automatically subdivided into four sectors around the center of mass. One sector (60°) corresponded to the valvular plane and was eliminated. The other sectors were in the left anterior oblique projection attributed to the anterolateral (120°) (REF_1), to the apicoposterior (60°) (REF_2), and to the anteroseptal (120°) areas (REF_3). Regional ejection fraction (REF) was calculated from end-diastolic and end-systolic counts as described above.

Regional Wall Motion Score

The left ventricular wall was divided arbitrarily into six segments, two segments each of the anteroseptal, apicoposterior, and anterolateral wall. Two experienced nuclear physicians graded the wall motion of each segment according to a regional wall motion score used in our laboratory in which 1 corresponds to normal wall motion; 2 to mild/moderate hypokinesia; 3 to severe hypokinesia; 4 to akinesia; and 5 to dyskinesia. For each patient, a total left ventricular regional wall motion score was calculated as the sum of the segmental scores.

Experimental Procedures

Patients were maintained on their cardiac medication, including the morning of the experimental day. Maximal bicycle exercise stress tests were performed in the supine position, the first without and the second with TEA. The workload was increased in steps by 25 W every fourth minute. The first exercise stress test was interrupted when the patient experienced moderate to severe chest pain. After a pause of approximately 2 h, the second stress test, with TEA, was performed; this test was identical to the first one with respect to workload and duration. Measurements were performed at rest, before (control) and after intravenous metoprolol (10–15 mg), and at the end of the first stress test. Before the second stress test additional intravenous metoprolol (5–10 mg) was given plus the appropriate amount of epidural bupivacaine, and 20 min thereafter basal measurements were performed. At the end of the second stress test the final measurements were performed. The first stress test is referred to as "control exercise" and the second as "TEA exercise."

Measurements included systolic (SAP) and diastolic (DAP) arterial pressure using a radial artery cannula, heart rate (HR), and ST-segment analysis of lead V_3 or V_5 using a Marquette CASE I electrocardiogram (Marquette Electronics, Milwaukee, Wis.), and left ventricular global and regional ejection fractions. Regional wall motion score was calculated during control exercise and TEA exercise. Rate-pressure product (RPP) was calculated as the product of SAP and HR. The difference in GEF and RPP for each patient, induced by TEA exercise compared with control exercise, was plotted against each other.

Statistics

All values are expressed as mean ± SEM. Data were analyzed by a one-way analysis of variance for repeated measurements followed by Newman–Keul's multiple range test for intergroup comparisons.

Results

Effects of metoprolol and metoprolol plus TEA on SAP, DAP, HR, RPP, GEF, REF_1, REF_2, and REF_3 at rest are shown in Table 2. Intravenous metoprolol or intravenous metoprolol plus TEA did not cause any

Table 3. Hemodynamics and Global and Regional Left Ventricular Function During Control Exercise and at an Identical Exercise With Thoracic Epidural Anesthesia

	SAP (mm Hg)	DAP (mm Hg)	HR (beats/min)	RPP (beats/min × mm Hg × 10^3)	GEF (%)	REF_1 (%)	REF_2 (%)	REF_3 (%)	RWMS	ST (mV)
Control exercise (metoprolol)	197 ± 10	84 ± 4	100 ± 6	20.0 ± 2	46.5 ± 4.9	46.0 ± 6.8	41.9 ± 6.0	43.5 ± 4.9	11.8 ± 1.0	−1.84 ± 0.22
TEA exercise (metoprolol + TEA)	160 ± 12^a	71 ± 6^a	94 ± 5	15.0 ± 2^a	52.8 ± 5.4^b	53.2 ± 6.1^b	47.7 ± 8.4	47.1 ± 3.7	8.8 ± 0.8^a	−1.03 ± 0.28^a

RWMS, regional wall motion score; ST, ST-segment depression. For all other abbreviations, see Table 2.
[a] $P < 0.01$, compared with control value.
[b] $P < 0.05$, compared with control value.

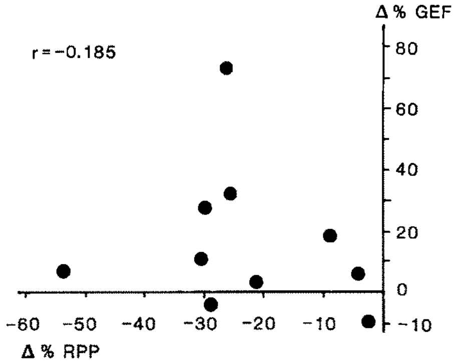

Figure 1. Relationship between the percentage difference in global ejection fraction (GEF) and the percentage difference in rate-pressure product (RPP) associated with exercise in the presence and absence of thoracic epidural anesthesia.

significant changes in the above-mentioned variables compared with control.

Data on the different variables during control exercise and during TEA exercise are shown in Table 3. During control exercise, GEF, REF_1, and REF_2 decreased significantly ($P < 0.01$) compared with resting control values, whereas GEF, REF_1, REF_2, and REF_3 were not significantly changed during TEA exercise compared with corresponding values at rest.

Compared with control exercise, SAP, DAP, and RPP, but not HR, were significantly lower during TEA exercise (Table 3). Furthermore, GEF and REF_1 (anterolateral) were significantly higher, and the regional wall motion score was significantly lower, during TEA exercise than during control exercise. ST-segment depression was also significantly lower during TEA exercise than during control exercise.

There was no correlation between the difference in GEF and the difference in RPP induced by TEA exercise compared with control exercise (Figure 1).

Discussion

Thoracic epidural anesthesia, including a blockade of cardiac sympathetic afferent and efferent fibers, effectively relieves chest pain caused by myocardial ischemia (2–4). It can be argued that blockade of cardiac pain fibers provides only symptomatic relief and therefore may be hazardous because it can abolish an important warning signal of myocardial ischemia. Thoracic epidural anesthesia used for this purpose can, therefore, be justified only if, in addition to its analgesic effect, it has beneficial myocardial effects, or at least does not harm the patient. There are several laboratory reports that have demonstrated beneficial effects of TEA during experimentally induced myocardial ischemia. Thus, it has been shown that TEA increases the endocardial to epicardial blood flow ratio (6), reduces the severity of myocardial ischemia (7), decreases myocardial infarct size (7), and reduces the incidence of malignant ventricular arrhythmias (8) during coronary occlusion in anesthetized animals.

In the present study, the effects of regional cardiac sympathetic blockade (TEA) on stress-induced ischemic left ventricular wall motion abnormalities and ST-segment changes have been studied in patients with coronary artery disease. The major findings were that TEA, in association with physical stress, improved ischemia-induced left ventricular global and regional wall motion abnormalities, which in turn was associated with less pronounced ST-segment depression than that seen during control exercise without TEA.

Our aim was to study patients with maximal or near maximal cardiac β-adrenergic receptor blockade, so that possible effects of cardiac sympathetic blockade on wall motion abnormalities with TEA would not be attributed directly to a reduced stimulation of β-receptors during exercise. Therefore, we selected patients in stable condition who were being treated with a β-blocker and in whom we also injected metoprolol before the exercise stress tests. Intravenous metoprolol or intravenous metoprolol plus TEA had no effect on HR at rest (Table 2). During exercise with TEA, HR was slightly but not significantly lower than during control exercise. Systolic arterial pressure and DAP, however, were both significantly lower during TEA exercise than during control exercise (Table 3). A possible explanation for the latter observation is that, although not studied in the present investigation, left ventricular outflow impedance was lower during exercise with TEA than it was during control exercise. Thus, TEA did not cause a sympathetic blockade involving only the heart, but probably involving other vascular beds as well. Accordingly, the RPP during exercise was significantly lower with TEA compared to control.

Radionuclide angiography is a valid and reproducible method for the determination of left ventricular ejection fraction as well as for qualitative and quantitative evaluation of regional wall motion (9–12). In healthy subjects, maximal dynamic physical exercise increases left ventricular GEF (13). However, in patients with multiple vessel coronary artery disease, GEF generally decreases due to myocardial ischemia (14). In the present study, GEF as well as REF_1 and REF_2 decreased significantly during control exercise; in contrast to exercise with TEA, during which global and regional wall motion were not significantly altered. The improvement in left ventricular global and regional function during exercise with TEA could be related to the decrease in left ventricular afterload per se because afterload reduction improves regional wall motion, especially when basal wall motion is reduced (15). Baron et al. recently showed in patients with coronary artery disease that lumbar epidural anesthesia without cardiac sympathectomy improved global and regional myocardial function at rest (16). This was attributed to reduction in afterload and/or to a decrease in myocardial oxygen requirement, which are in turn related to the decrease in afterload. In the present study, the most likely explanation for the improvements in left ventricular global and regional function during TEA exercise is that TEA beneficially affects the oxygen supply/demand ratio in the ischemic area mainly by reducing myocardial oxygen demand, as reflected by the lower RPP. This was supported by significant attenuation of ischemic ST-segment changes in anterolateral leads (V_3 or V_5) associated with an improved regional wall motion in the corresponding area (REF_1). We have recently shown in patients with unstable angina and ischemic chest pain at rest that pain relief with TEA is associated with a decrease in the major determinants of myocardial oxygen demand, without jeopardizing coronary perfusion pressure (5). In some of our patients, TEA induced less pronounced ST-segment depression and myocardial lactate production. It is therefore likely that TEA may have an antiischemic effect during both stress-induced and spontaneously induced myocardial ischemia by reducing myocardial oxygen demand (17).

One would expect that the improvement in GEF during exercise with TEA, when compared with GEF during exercise without TEA, would be most pronounced in patients in whom TEA caused the greatest reduction in RPP. However, in the present study there was no correlation between the difference in GEF and the difference in RPP induced by TEA exercise compared with control exercise, as can be seen in Figure 1. One could therefore speculate that attenuation of myocardial ischemia by TEA, in the present study, was caused not only by a reduction in myocardial oxygen demand but also by improved perfusion of the ischemic area. We have recently determined the effect of cardiac sympathetic blockade by TEA on the diameter of the lumina of normal and diseased portions of epicardial coronary arteries by quantitative coronary angiography in patients with severe coronary artery disease (18). Thoracic epidural anesthesia significantly increased the diameter of stenotic segments, whereas there was no effect on nonstenotic segments. Also, in humans the activation of the sympathetic nervous system by isometric handgrip or cold pressor test constricts both normal and diseased coronary arteries (19). Furthermore, in patients with coronary artery disease, the intracoronary administration of phentolamine causes less exercise-induced ST-segment depression than that seen at an identical workload without phentolamine (20). It is therefore tempting to suggest that the antiischemic effects of TEA during stress-induced myocardial ischemia is also caused by a blunting of a sympathetically, α-adrenoceptor-mediated vasoconstriction of stenotic epicardial arteries, one that also improves perfusion of the ischemic areas.

In conclusion, in patients with coronary artery disease subjected to physical stress, high TEA improves global and regional left ventricular function while diminishing associated changes in ST segments.

References

1. Bishop VS, Malliani A, Thorén P. Cardiac mechanoreceptors. In: Shephard JT, Abboud FM, eds. Handbook of physiology. The cardiovascular system. Part III. Baltimore: Williams & Wilkins, 1983:497–555.

2. Tevelenok YUA. Peridural anesthesia in the acute period of myocardial infarction. Anesteziol Reanimatol 1977;3:36–9.
3. Toft P, Jörgensen A. Continuous thoracic epidural analgesia for the control of pain of myocardial infarction. Intens Care Med 1987;13:388–9.
4. Blomberg S, Curelaru I, Emanuelsson H, Herlitz J, Pontén J, Ricksten S-E. Thoracic epidural anaesthesia in patients with unstable angina pectoris. Eur Heart J 1989;10:437–44.
5. Blomberg S, Emanuelsson H, Ricksten S-E. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 1989;69:558–62.
6. Klassen GA, Bramwell RS, Bromage PR et al. Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology 1980;52:8–15.
7. Davis RF, de Boer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 1986;65:711–7.
8. Blomberg S, Ricksten S-E. Thoracic epidural anaesthesia decreases the incidence of ventricular arrhythmias during acute myocardial ischemia in the anaesthetized rat. Acta Anaesthesiol Scand 1988;32:173–8.
9. Marshall RR, Berger HJ, Costin JC, et al. Assessment of cardiac performance with quantitative radionuclide angiography: sequential left ejection fraction, normalized left ventricular ejection rate and regional wall motion. Circulation 1977;56:820–9.
10. Heidendal GAK, Dezemer PD, Koopman PAR, et al. Reproducibility of ejection fraction measurements by gated equilibrium blood pool scintigraphy. Eur J Nucl Med 1983;8:467–70.
11. Papapietro SE, Yester MV, Logic JR, et al. Method for quantatative analysis of regional left ventricular function with first pass and gated blood pool scintigraphy. Am J Cardiol 1981;47: 618–25.
12. Neuman P, Schicha H, Tebbe U, Krenzer M, Emrich D. Analysis of left ventricular regional mobility: a comparison of different methods. Eur J Nucl Med 1984;9:205–8.
13. Manyari DE, Kostuk WJ. Left and right ventricular function at rest and during bicycle exercise in the supine and sitting positions in normal subjects and patients with coronary artery disease. Am J Cardiol 1983;51:36–42.
14. Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cine-angiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 1977;296:839–44.
15. Okada RD, Boucher CA, Strauss HW, Pohost GM. Exercise radionuclide imaging approaches to coronary artery disease. Am J Cardiol 1980;46:1188–204.
16. Baron JF, Coriat P, Mundler O, Fauchet M, Bousseau D, Viars P. Left ventricular global and regional function during lumbar epidural anesthesia in patients with and without angina pectoris: influence of volume loading. Anesthesiology 1987;66: 621–7.
17. Rosenbaum SH, Barash PG. Is anesthesia therapeutic? (editorial). Anesth Analg 1989;69:555–7.
18. Blomberg S, Emanuelsson H, Kvist H, et al. Effects of thoracic epidural anesthesia on coronary arteries and arterioles in patients with coronary artery disease. Anesthesiology 1990 (in press).
19. Raizner AE, Chahine RA, Isahimori T, et al. Provocation of coronary artery spasm by the cold pressor test. Hemodynamic, arteriographic and quantitative angiographic observations. Circulation 1980;62:925–32.
20. Berkenboom GM, Abramowicz M, Vandermolen P. Role of alpha-adrenergic coronary tone in exercise-induced angina pectoris. Am J Cardiol 1986;57:195–8.

Controlled Hypotension With Adenosine or Sodium Nitroprusside During Cerebral Aneurysm Surgery: Effects on Renal Hemodynamics, Excretory Function, and Renin Release

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ZÄLL S, EDÉN E, WINSÖ I, VOLKMANN R, SOLLEVI A, RICKSTEN S-E. Controlled hypotension with adenosine or sodium nitroprusside during cerebral aneurysm surgery: effects on renal hemodynamics, excretory function, and renin release. Anesth Analg 1990;71:631–6.

Adenosine, a potent vasodilator both in animals and in humans, has been used to produce controlled hypotension in patients, especially during cerebral aneurysm surgery. However, in animals adenosine by intrarenal infusion decreases renal blood flow (RBF), glomerular filtration rate (GFR), urine flow, and causes an inhibition of renin secretion. In this study we evaluated the effect of adenosine on RBF in patients ($n = 15$) scheduled for cerebral aneurysm surgery who had been anesthetized with a modified neurolept-anesthesia during controlled hyperventilation. Perioperative hypotension was achieved with infusion of adenosine ($252.8 \pm 55.8\ \mu g \cdot kg^{-1} \cdot min^{-1}$) ($n = 8$) or sodium nitroprusside ($2.5 \pm 0.8\ \mu g \cdot kg^{-1} \cdot min^{-1}$) ($n = 7$). Mean arterial pressure was lowered by 25%–30%, to approximately 60–70 mm Hg, in both groups. Glomerular filtration rate and RBF were measured using standard renal clearance methods for ^{51}Cr-ethylenediaminetetraacetic acid and paraaminohippuric acid. Urine and blood samples were collected during normotension before and after a bolus dose of hypertonic mannitol, during hypotension, and during normotension after clipping of the aneurysm. Adenosine induced a marked decrease in GFR (−91%) and RBF (−92%), and a pronounced increase in renal vascular resistance. Sodium nitroprusside caused a significantly ($P < 0.01$) less pronounced decrease in GFR (−24%) and RBF (−36%), but did not affect renal vascular resistance. After discontinuation of the hypotensive agents, GFR returned to baseline levels in both groups. Renal blood flow, however, increased above baseline after discontinuation of adenosine (+93%) but not after sodium nitroprusside. Sodium nitroprusside increased renin secretion, which was not seen with adenosine. Four patients in the adenosine group developed reversible atrioventricular conduction disturbances. We conclude that adenosine-induced hypotension during cerebral aneurysm surgery prevents renin release and induces a reversible renal vasoconstriction mainly involving preglomerular resistance vessels and thereby decreasing RBF and GFR.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—adenosine, nitroprusside. KIDNEY, FUNCTION—induced hypotension. PHARMACOLOGY—nitroprusside, adenosine.

During the dissection and clipping of cerebral aneurysms, controlled hypotension is often used to reduce the aneurysm wall tension in order to minimize the risk of rupture and bleeding (1). Several vasodilators, including sodium nitroprusside (SNP) (2) and nitroglycerin (3), have been used for this purpose. However, these drugs have disadvantages such as cyanide toxicity (4), tachyphylaxis (2,5,6), rebound hypertension (7), increased intracranial pressure (3,8), and methemoglobinemia (3). The use of exogenous adenosine administration to achieve controlled hypotension during neurosurgery in humans has attracted considerable interest because it is characterized by a rapid induction of a stable level of hypotension, which is rapidly and spontaneously reversed when administration is discontinued, and has shown no evidence of hematologic or biochemical toxicity (9).

Animal studies have, however, shown that intrarenal adenosine infusion causes a dose-dependent

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Supported by grants from the Medical Research Council (No. 08682 and 07485) and Hässle AB, Mölndal, Sweden.

Presented in part at the Annual Meeting of Swedish Society of Anesthesia and Intensive Care, Uppsala, Sweden, September 1989.

Received from the Department of Anesthesia and Intensive Care, Sahlgren's Hospital and Karolinska Hospital, University of Gothenburg and Stockholm; and the Department of Clinical Physiology, Sahlgren's Hospital, Gothenburg, Sweden. Accepted for publication July 23, 1990.

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transient reduction in renal blood flow (RBF) (10–16), sustained decrease in glomerular filtration rate (GFR) (10,11,13–16), renal cortical vasoconstriction (10–15), and inhibition of renin secretion (10,11,15–18), as well as decreased urinary output (6,10,15).

Therefore, the aim of this study was to evaluate the effects of adenosine on renal function and renin release, and to compare them with the effects of SNP when used for controlled hypotension during cerebral aneurysm surgery.

Patients and Methods

The investigation was approved by the Ethical Committee of the University of Gothenburg, Sweden, and informed consent was obtained from the patients.

Fifteen patients scheduled for cerebral aneurysm surgery were studied. None of the patients was hypertensive, and none was on any chronic medication. The patients were randomly allocated to receive either adenosine (20 mmol/L, 5.3 mg/mL in 5% mannitol) (n = 8) or SNP (Nipride, Roche, 100 μg/mL) (n = 7) for induced hypotension according to a computer-generated list. Criteria for inclusion in the study were no history of renal, hepatic, or heart disease, and age below 70 yr. Mean age was 44.1 ± 2.9 yr (range, 34–51) in the adenosine group and 47.7 ± 4.4 yr (range, 33–65) in the SNP group.

One hour before the operation, the patients were premedicated with diazepam (5–10 mg IV). Atropine (0.25–0.50 mg IV) was given before induction of anesthesia. Induction of anesthesia was with 2–5 mg/kg thiopental followed by 0.1–0.2 mg fentanyl. Pancuronium bromide (0.1 mg/kg) was given to facilitate tracheal intubation. Anesthesia was maintained with supplemental doses of fentanyl (total dose, 1.1–2.0 mg) and droperidol (total dose, 2.5–10 mg) as required. The patients were mechanically hyperventilated with 70% nitrous oxide in oxygen to maintain Pco_2 values at approximately 3.5 kPa (30 mm Hg). Catheters were placed in the radial artery for monitoring blood pressure and sampling blood. Two central venous catheters were inserted via the left basilic vein and the right jugular vein for monitoring central venous pressure (CVP) and infusion of drugs. All patients had an intravesical catheter for continuous monitoring of urine flow. Nimodipine, a calcium-channel blocker that is distinguished by vasodilatory activity most specific to the cerebral vessels (19), was given in a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ perioperatively to four patients in the SNP group and to two patients in the adenosine group to prevent cerebral vasospasm.

All patients received 1.0–1.5 L of 5% glucose perioperatively. The average amount of mannitol (150 mg/mL) given was 801 ± 53 mg/kg in the SNP group and 939 ± 78 mg/kg in the adenosine group (NS). Blood loss during the surgical procedure amounted to 10.5 ± 3.9 mL/kg in the SNP group and 9.0 ± 2.2 mL/kg in the adenosine group (NS).

To study the effects of SNP or adenosine on RBF and GFR, standard urinary clearances of ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) and paraaminohippuric acid (PAH) were used (20,21). Priming injections of PAH and ^{51}Cr-EDTA were given immediately after the induction of anesthesia, followed by continuous intravenous infusions of PAH and ^{51}Cr-EDTA. The amounts of ^{51}Cr-EDTA and PAH given were calculated based on the patient's body surface, age, and preoperative serum creatinine concentration. Equilibration time before the start of the study was 35–40 min. Arterial plasma samples for measurements of PAH and ^{51}Cr-EDTA were taken at the beginning and end of each urine collection period. At the end of each urine collection period, the bladder was rinsed with 100 mL of sterile water and emptied by aspiration and gentle suprapubic compression. Renal blood flow was derived from the formula RBF = renal clearance of PAH/(1 − hematocrit), and renal vascular resistance (RVR), from the formula RVR = MAP − CVP/RBF, where MAP is mean arterial pressure. All renal data were normalized to a body surface area of 1.73 m^2. Blood samples for analysis of plasma renin activity (PRA) (17) in both groups and plasma levels of adenosine metabolites (hypoxanthine, xanthine, and uric acid) (15,22) in the adenosine group were measured at the end of each period.

After the induction of anesthesia, continuous measurements of systolic arterial pressure, MAP, diastolic arterial pressure, CVP, heart rate, and urine flow were made, and blood samples were taken, as described above during four consecutive 30-min urine collection periods: (A) during normotension before mannitol; (B) during normotension after mannitol; (C) during hypotension; and (D) during normotension. During period C (hypotension), MAP was 25%–30% below baseline levels (period A). Two patients in the adenosine group had two consecutive 30-min periods of hypotension.

A 12-lead electrocardiogram was used pre- and postoperatively. During surgery, the electrocardiogram was continuously tape-recorded, and it was submitted to computerized analysis postoperatively (23).

Values are presented as mean ± SEM. Differences between the two groups were calculated by two-way analysis of variance, followed by the Newman–Keuls

Table 1. Arterial Plasma Levels of Adenosine Metabolites Before, During, and After Adenosine Administration

	Before ADO	During ADO	After ADO
Uric acid (μmol/L)	101.3 ± 38.9	279.7 ± 66.2[a]	260.2 ± 60.7
Hypoxanthine (μmol/L)	0.9 ± 0.3	11.2 ± 3.5[a]	3.4 ± 0.7
Xanthine (μmol/L)	1.7 ± 0.8	131.6 ± 35.4[a]	70.9 ± 24.7

ADO, adenosine.

[a] $P < 0.05$, before adenosine versus during adenosine.

multiple range test (24). A P value less than 0.05 was considered statistically significant.

Results

In both groups, MAP was lowered by approximately 25%–30% during the hypotensive period. The initial dose of SNP used was 1.8 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the dose required just before discontinuing the infusion was 2.6 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.05$). The corresponding values for adenosine were 218 ± 51 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 266 ± 56 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.05$). Plasma concentrations of adenosine metabolites increased significantly above baseline levels during adenosine infusion and partially returned to baseline levels during the following normotensive period (Table 1). Pulse pressure was significantly greater during adenosine than during SNP infusion. After discontinuation of the vasodilators, MAP and diastolic arterial pressure were higher in the SNP group, whereas other hemodynamic variables did not differ between the two groups at any period (Table 2).

Glomerular filtration rate and RBF were significantly lower, and renal vascular resistance was significantly greater, during adenosine than during SNP-induced hypotension (Table 3). However, during the normotensive period D, RBF was significantly higher in the adenosine than in the SNP group. Plasma renin activity levels were significantly greater with SNP than with adenosine infusion, which was not associated with any change in PRA levels. Other renal variables did not differ between the two groups at any period.

Two patients had a second period of adenosine-induced hypotension. The mean values of GFR for these two patients during the first and second hypotensive periods were 3.0 and 2.3 mL/min, respectively, and the corresponding mean values of RBF were 21.1 and 98.2 mL/min, respectively.

The pre- and postoperative values of serum creatinine were 80.9 ± 2.8 μmol/L and 67.3 ± 3.4 μmol/L, respectively, in the SNP group ($P < 0.01$). The corresponding values for the adenosine group were 72.0 ± 4.2 μmol/L (NS) and 70.1 ± 3.3 μmol/L (NS).

During adenosine-induced hypotension, one patient developed first-degree atrioventricular block and two patients a nodal rhythm. These arrhythmias were seen at infusion rates ranging from 147 to 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but were not hemodynamically important and disappeared after discontinuation of adenosine. One patient was excluded from the study because of development of third-degree atrioventricular block for 15 s followed by atrial flutter for 26 min. This patient received 590 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of adenosine, an extremely high dose that failed nevertheless to induce hypotension. The adenosine infusion was immediately stopped, and hypotension was induced with trimethaphan. This incident did not affect the clinical course of the patient. Postoperative electrocardiogram and myocardial enzymes in this patient were normal. In no patient were significant ST-T changes seen during either adenosine- or SNP-induced hypotension.

Discussion

To study the effects of adenosine- or SNP-induced hypotension on renal function during neurosurgery, we used standard techniques for urinary clearance of PAH and ^{51}Cr-EDTA. These methods have been used for many years and are well established and accepted, even under conditions where RBF and GFR are reduced (20,21). We did not measure the renal extraction of PAH because we did not consider it practical or ethically justified to perform renal vein catheterization during this clinical study. Because we did not evaluate the renal extraction of PAH, it may be argued that RBF could have been underestimated, especially during adenosine-induced hypotension, which was associated with low urinary clearance values of PAH. However, a previous study (25) in dogs with experimental hemorrhagic shock showed that RBF could be reduced to as low as 3% of control without decreasing the renal extraction of PAH. Previous studies investigating renal function perioperatively during neurolept-anesthesia have shown that this method is reliable even during surgical conditions (26). The values of urine flow, GFR, and RBF during period A, in the present study, are in line with those presented in other studies where renal function has been studied during neurolept-anesthesia in connection with surgery (26).

The main findings of the present study were that

Table 2. Hemodynamic Changes Before, During, and After Adenosine, and Sodium Nitroprusside-Induced Hypotension

	ADO				SNP			
	A	B	C	D	A	B	C	D
SAP (mm Hg)	119.7 ± 7.0	125.6 ± 5.5	98.0 ± 3.9	120.0 ± 4.7	117.4 ± 3.3	131.2 ± 4.7	90.2 ± 2.7	131.9 ± 5.9
MAP (mm Hg)	89.5 ± 3.7	90.2 ± 3.3	61.7 ± 2.6	84.3 ± 3.0^a	87.0 ± 1.2	92.7 ± 5.3	65.3 ± 2.5	73.0 ± 2.6
DAP (mm Hg)	74.3 ± 2.5	73.0 ± 2.6	44.5 ± 2.3	66.5 ± 3.6^a	70.5 ± 1.7	72.5 ± 6.0	52.9 ± 3.3	76.6 ± 3.9
PP (mm Hg)	45.4 ± 5.5	52.6 ± 4.6	53.5 ± 3.3^a	53.5 ± 5.6	46.8 ± 4.1	58.8 ± 4.9	37.2 ± 3.7	55.1 ± 6.3
HR (beats/min)	86.4 ± 5.0	86.0 ± 7.3	87.8 ± 5.4	79.5 ± 3.9	82.0 ± 3.4	77.1 ± 5.1	80.3 ± 4.5	71.3 ± 3.9
CVP (mm Hg)	3.4 ± 1.0	2.9 ± 1.0	3.6 ± 0.9	3.9 ± 0.9	1.9 ± 1.0	2.6 ± 1.0	2.6 ± 1.2	2.9 ± 1.2

ADO, adenosine; SNP, sodium nitroprusside; A, normotension before mannitol; B, normotension after mannitol; C, hypotension; D, normotension; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; PP, arterial pulse pressure; HR, heart rate; CVP, central venous pressure.

$^a P < 0.05$, adenosine versus sodium nitroprusside.

Table 3. Renal Hemodynamics, Renal Function, and Levels of Plasma Renin Activity Before, During, and After Adenosine- and Sodium Nitroprusside-Induced Hypotension

	ADO				SNP			
	A	B	C	D	A	B	C	D
UF (mL/min)	5.1 ± 0.9	8.6 ± 2.2	0.4 ± 0.1	3.8 ± 0.6	5.0 ± 2.3	11.7 ± 3.5	2.8 ± 0.5	2.6 ± 0.5
GFR (mL/min)	85.3 ± 68	73.4 ± 10.7	7.4 ± 4.6^a	75.2 ± 7.9	100.1 ± 11.0	99.4 ± 13.6	76.5 ± 12.7	108.0 ± 23.1
RBF (mL/min)	692 ± 81	626 ± 133	52 ± 18^a	1340 ± 215^a	1047 ± 180	771 ± 124	671 ± 43	694 ± 123
RVR (mm Hg·min·L^{-1})	0.14 ± 0.03	0.24 ± 0.1	2.84 ± 1.2^a	0.07 ± 0.01	0.10 ± 0.03	0.13 ± 0.01	0.10 ± 0.01	0.15 ± 0.02
PRA (μmol/L)	1.2 ± 0.2	1.3 ± 0.4	1.5 ± 0.6	2.0 ± 0.7	2.4 ± 0.7	1.8 ± 0.4	8.7 ± 4.2^a	4.9 ± 1.6

ADO, adenosine; SNP, sodium nitroprusside; A, normotension before mannitol; B, normotension after mannitol; C, hypotension; D, normotension; UF, urine flow; GFR, glomerular filtration rate; RBF, renal blood flow; RVR, renal vascular resistance; PRA, plasma renin activity.

$^a P < 0.01$, adenosine versus sodium nitroprusside.

induced hypotension with adenosine induced a marked decrease in GFR and RBF compared to SNP-induced hypotension, followed by a pronounced increase in RBF during period D (after adenosine), which was not seen after discontinuation of SNP. In a previous study of renal function in humans during adenosine infusion, Sollevi (10) found that low doses (40–50 μg·kg^{-1}·min^{-1}) of intravenous adenosine in awake and healthy volunteers did not affect RBF or GFR, whereas in some subjects urine flow rate was reduced by 25%–40% in association with a reduction of free water clearance. However, hypotensive doses of adenosine have, in connection with neurosurgery, previously been associated with a marked reduction of urine flow rate (27), as also seen in the present study. It is also obvious from the present study that hypotensive doses of adenosine decrease urine flow mainly by a renal vasoconstriction with a pronounced decrease in GFR.

A large number of animal studies have been performed to evaluate the renal effects of adenosine (10,11,13–16,28). Adenosine injected as a bolus into the renal artery produces a prompt and dose-related decrease in RBF (15). However, during continuous infusion of adenosine into the renal artery there is generally a biphasic response in RBF: a transient decrease in RBF that wanes and within 5–10 min returns to or above preinfusion levels (15). It has been suggested that the apparent wane of the initial vasoconstriction is some unknown secondary vasodilator response superimposed on the initial vasoconstriction (15). Adenosine infusion also decreases GFR due to an increased resistance of the afferent arterioles of superficial nephrons with a consequent decrease in glomerular capillary hydrostatic pressure (14). It has been suggested that the vasoconstrictive action of adenosine is mediated by angiotensin II (28). Glomerular filtration rate has been reported to be consistently decreased during exogenous adenosine infusion in the face of a normal or even increased total RBF (15). It has therefore been suggested that adenosine may act to decrease GFR also by direct dilation of efferent arterioles of deeper nephrons in a later phase of the adenosine infusion (13). In the present study, the decrease in MAP by 25%–30% with adenosine was associated with a 91% decrease in GFR, indicating that the adenosine-induced renal vasoconstriction was caused mainly by an increased afferent glomerular arteriolar resistance. The present study cannot exclude the possibility that adenosine also induces a biphasic response in RBF in humans during a certain period of time. In fact, two patients given adenosine were exposed to induced hypotension for a second period of 30 min. During this second hypotensive period, RBF was higher, whereas GFR was virtually unchanged compared to the first hypotensive period, which may indicate that adenosine infusion induces a biphasic response of RBF accompanied by an unchanged GFR also in humans. It would therefore be of interest to induce hypotension with adenosine for longer periods and to study whether there is a biphasic RBF response concomitant with a consistent decrease in GFR during adenosine-induced hypotension. In the present study of mild adenosine-induced hypotension for only 30 min, we did not investigate the long-term effects on renal function. The postoperative serum creatinine level was, however, not significantly different from the preoperative value in the adenosine group, which might indicate that short periods of adenosine-induced hypotension does not cause any long-term sequelae, in terms of renal function. Whether this is true also for longer periods of profound adenosine-induced hypotension remains to be answered.

During the normotensive recovery period, after discontinuation of adenosine infusion, there was a marked increase in RBF whereas GFR was restored to prehypotensive values, indicating that the renal vasodilation after adenosine was caused mainly by a decreased efferent glomerular arteriolar resistance. This renal hyperemia after adenosine has previously been reported in animals, but its cause remains to be defined (13,14). It is possible that this renal vasodilation represents a reactive hyperemic response to the relative renal ischemia induced by adenosine.

Sodium nitroprusside-induced hypotension in patients undergoing neurosurgery increases PRA, which in turn causes tachyphylaxis and rebound hypertension in some patients due to activation of the renin angiotensin system (7). In the present study, SNP-induced hypotension caused a significant increase in PRA, whereas adenosine infusion did not change PRA, which is in accordance with another recent clinical study (18). Furthermore, we noticed a mild rebound hypertension after SNP infusion was discontinued, but no rebound hypertension was recorded after adenosine administration. However, in both groups there was a significant increase in the required infusion rate of the hypotensive agent.

Pulse pressure was significantly higher during adenosine compared to SNP-induced hypotension. This difference probably reflects the limited effect of adenosine on venous capacitance vessels, in contrast to SNP, with maintained filling pressures and a hyperkinetic circulation during adenosine-induced hypotension (10). The higher systolic arterial pressure during adenosine-induced hypotension may, however, counteract the beneficial effects of a reduced MAP in terms of wall tension of the cerebral aneurysm.

There were no signs of myocardial ischemia during adenosine-induced hypotension, as judged by unchanged ST-T segments in any patient. Atrioventricular conduction disturbances were noticed during adenosine administration in four patients during high infusion rates of adenosine that rapidly disappeared when infusion rates were lowered.

One of our patients received a very high infusion rate of adenosine (590 $\mu g \cdot kg^{-1} \cdot min^{-1}$), without producing the desired level of hypotension, but instead a third-degree atrioventricular block. The reason for the ineffective hypotensive effect is not evident but could be due to a reflex increase in cardiac output, in accordance with hemodynamic responses seen in awake healthy subjects (29).

In summary, we have shown that adenosine-induced hypotension, in striking contrast to nitroprusside, inhibits renin release and induces profound decreases in RBF and GFR caused by predominant afferent glomerular arteriolar vasoconstriction. When adenosine infusion was discontinued, GFR returned to, whereas RBF increased above, baseline levels. The effects of adenosine-induced hypotension on renal function would therefore suggest that its use be limited to short periods of hypotension. Furthermore, adenosine should not be used in patients with impaired renal function.

We thank Professor Gerald F. DiBona, Department of Internal Medicine, The University of Iowa College of Medicine, for his constructive criticism of this manuscript.

References

1. Yashon D, Magness AP, Vise WM. Systemic hypotension in neurosurgery. J Neurosurg 1975;43:579–89.
2. Rudehill A, Gordon E, Lagerkranser M. Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. Acta Anesthesiol Scan 1979;23:404–10.
3. Hill NS, Antman EM, Green HL, Alpert JS. Intravenous nitroglycerin: a review of pharmacology, indications, therapeutic effects and complications. Chest 1981;79:69–76.
4. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45:340–54.
5. Amaranath L, Kellermeyer WF Jr. Tachyphylaxis to sodium nitroprusside. Anesthesiology 1976;44:345–8.
6. Norlen K. Central and regional haemodynamics during controlled hypotension produced by adenosine, sodium nitroprusside and nitroglycerine. Br J Anaesth 1988;61:186–93.
7. Khambattah HJ, Stone GJ, Khan E. Hypertension during

anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.

8. Turner JM, Powell D, Gibson RM, McDowall DG. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimethaphan. Br J Anaesth 1977;49:419–25.
9. Sollevi A, Lagerkranser M, Irestedt L, Gordon E, Lindqvist C. Controlled hypotension with adenosine in cerebral aneurysm surgery. Anesthesiology 1984;61:400–5.
10. Sollevi A. Cardiovascular effects of adenosine in man: possible clinical implications. Prog Neurobiol 1986;27:319–49.
11. Spielman WS, Arend LJ, Forrest JN Jr. The renal and epithelial actions of adenosine. In: Gerlach E, Becker BF, eds. Topics and perspectives in adenosine research. Berlin, Heidelberg: Springer Verlag, 1987:249–60.
12. Crystal GJ, Rooney MW, Ramez Salem M. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine induced controlled hypotension. Anesth Analg 1988;67:211–8.
13. Hall JE, Granger JP, Hester RL. Interactions between adenosine and angiotensin II in controlling glomerular filtration. Am J Physiol 1985;248:340–6.
14. Osswald H, Spielman WS, Knox FG. Mechanism of adenosine-mediated decreases in glomerular filtration rate in dogs. Clin Res 1978;43:465–9.
15. Spielman WS, Thompsson CI. A proposed role for adenosine in the regulation of renal hemodynamics and renin release. Am J Physiol 1982;242:423–35.
16. Tagawa H, Vander AJ. Effects of adenosine compounds on renal function and renin section in dogs. Circ Res 1970;26:327–38.
17. Lagerkranser M, Sollevi A, Irestedt L, Tidgren B, Andreen M. Renin release during controlled hypotension with sodium nitroprusside, nitroglycerin and adenosine. A comparative study in the dog. Acta Anaesthesiol Scand 1985;29:45–9.
18. Öwall A, Lagerkranser M, Sollevi A. Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism during cerebral aneurysm surgery. Anesth Analg 1988;67:228–32.
19. Kazda S, Towart R. Nimodipine: a new calcium antagonistic drug with a preferential cerebrovascular action. Acta Neurochir (Wien) 1982;63:259–65.
20. Brun C. A rapid method for the determination of para-amino hippuric acid in kidney function tests. Lab Clin Med 1951;37:955–8.
21. Aurell M, Ditzel J. Renal clearance of ^{51}Cr-EDTA-complex; a comparison between continuous infusion and single injection techniques. In: Proceedings of the Seventh International Congress on Clinical Chemistry, Geneva/Evian, 1969. Volume 3: Hormones, lipids, and miscellaneous. Basel: Karger, 1970: 405–13
22. Schweinsberg PD, Loo TL. Simultaneous analysis of ATP, ADP, AMP and other purines in human erythrocytes by HPLC. J Chromatogr 1980;181(1):103–7.
23. Falk K-J, Angelhed J-E, Bjurö TI. Real-time processing of multiple-lead exercise electrocardiogram. Med Progr Technol 1982;8:159–74.
24. Zar JH. Biostatistical analysis. Englewood Cliffs, N.J.: Prentice-Hall, 1974:130–81.
25. Phillips RA, Dole, VP, Hamilton PB, Emersson K Jr, Archibald RM, Van Slyke, DD. Effects of acute hemorrhagic and traumatic shock on renal functions of dogs. Am J Physiol 1946;145: 314–36.
26. Järnberg PO, Santesson J, Eklund J. Renal function during neurolept anesthesia. Acta Anesth Scand 1978;22:167–72.
27. Öwall A, Gordon E, Lagerkranser M, Lindqvist C, Rudehill A, Sollevi A. Clinical experience with adenosine for controlled hypotension during cerebral aneurysm surgery. Anesth Analg 1987;66:229–34.
28. Hall JE, Granger JP. Adenosine alters glomerular filtration control by angiotensin II. Am J Physiol 1986;250:917–23.
29. Bush A, Busst CM, Clarke B, Barnes PJ. Effects of infused adenosine on cardiac output and systemic resistance in normal subjects. Br J Clin Pharmacol 1989;27:165–71.

ANESTH ANALG 637
1990;71:637–44

Pulmonary Hypertension After Heparin-Protamine: Roles of Left-Sided Infusion, Histamine, and Platelet-Activating Factor

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HABAZETTL H, CONZEN PF, VOLLMAR B, YEKEBAS E, GUTMANN R, HOBBHAHN J, BRENDEL W, PETER K. Pulmonary hypertension after heparin-protamine: roles of left-sided infusion, histamine, and platelet-activating factor. Anesth Analg 1990;71:637–44.

Severe pulmonary hypertension after protamine neutralization of heparin is an infrequent but life-threatening event following cardiopulmonary bypass. The effect of left ventricular infusion of protamine on pulmonary hypertension as well as a possible role of platelet-activating factor (PAF) or histamine in the heparin-protamine reaction was investigated in 30 pigs in four different groups during general anesthesia. Group 1 animals received 250 IU/kg heparin, followed by 100 mg protamine intravenously after 15 min. In group 2 protamine was infused into the left ventricle. Group 3 animals received the histamine H_1- and H_2-antagonists clemastine and ranitidine 5 min before protamine infusion. In group 4 the PAF receptor blocker WEB 2086 was given 5 min before protamine. Platelet-activating factor was measured by a bioassay in serum samples of group 1 and group 4 animals. In all four groups protamine caused severe pulmonary hypertension, thromboxane A_2 release, and a transient decrease in leukocyte counts. No PAF release was detected after protamine infusion. Neither left ventricular infusion of protamine nor histamine or PAF antagonists prevented or attenuated the reactions after protamine infusion. The authors conclude that left ventricular infusion of protamine provides no protection from pulmonary hypertension, and that histamine and PAF are not involved in the acute pulmonary vasoconstriction after protamine neutralization of heparin.

Key Words: BLOOD, COAGULATION—heparin, protamine.

The adverse hemodynamic effects of heparin neutralization by protamine, acute pulmonary vasoconstriction, and systemic hypotension occur infrequently in patients but can result in life-threatening circulatory disorders. Horrow, in two comprehensive reviews, defined three different types of circulatory reactions to protamine reversal of heparin: type I, systemic hypotension from rapid injection; type II, anaphylactoid responses; and type III, catastrophic pulmonary vasoconstriction (1,2). Severe type III reactions can be life-threatening complications after otherwise uneventful cardiac operations (3), and a number of recently published studies deal with the mechanisms and the prevention of pulmonary hypertension after heparin-protamine.

In humans, thromboxane A_2 generation is associated with pulmonary vasoconstriction (4), and experiments in awake sheep (5) and anesthetized pigs (6,7) have confirmed the role of arachidonate products and, predominantly, of thromboxane A_2 in this reaction. A study by Morel and coworkers (5) also suggests that complement-mediated activation of leukocytes might cause activation of arachidonic acid via the formation of oxygen free radicals and lipid peroxidation. Dimethylthiourea, the substance that successfully inhibited thromboxane release in that study, however, cannot be used in humans because of its well-known toxicity. Moreover, it has a wide variety of side effects and may have affected the heparin-protamine reaction by some mechanism different from the scavenging of H_2O_2. Thus, further research is required for a conclusive definition of the mechanisms by which the arachidonic acid cascade and, finally, thromboxane synthetase are activated. Also, a therapeutic principle that allows prevention of hep-

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Supported by the Deutsche Forschungsgemeinschaft, grant Co 123/2-1.

Received from the Institute of Surgical Research and the Institute of Anesthesiology, Ludwig-Maximilians-University, Munich, Germany. Accepted for publication August 3, 1990.

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arin-protamine reactions without major side effects has not yet become clinically available.

The aim of the present study, therefore, was to investigate the role of further mediators that, as judged from the patterns of their actions, might participate in heparin-protamine-related pulmonary hypertension. This was done by measuring serum activities of platelet-activating factor (PAF), a potent activator of platelets in vitro and in vivo (8), before and after heparin antagonization by protamine. The effect of pretreatment with histamine and PAF receptor blockers on the incidence and severity of the heparin-protamine reaction in the anesthetized pig model of pulmonary hypertension was studied. In a further series of experiments the potentially protective effect of intraarterial versus intravenous infusion of protamine was tested, as presently available studies addressing this issue are inconclusive (2).

Methods

Animal Preparation

Upon approval by the animal-care committee, experiments were performed in 30 pigs with a mean body weight of 27 kg. Anesthesia was induced with ketamine (10 mg/kg), flunitrazepam (0.1 mg/kg), and atropine (0.5 mg). The animals were tracheotomized and ventilated mechanically with a mixture of oxygen in nitrous oxide to maintain arterial Po_2 between 100 and 120 mm Hg. The tidal volume was set to maintain end-expiratory carbon dioxide at 4.5 vol%, and a positive end-expiratory pressure of 3 cm H_2O prevented atelectasis. Adequate anesthetic depth was maintained by enflurane (0.5–1.0 vol%, inspiratory) and fentanyl (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$).

Large-bore polyethylene catheters in the inferior vena cava and the abdominal aorta served for drug infusion, pressure measurements, and blood sampling. Two flotation-directed, balloon-tipped catheters of different sizes were placed in the pulmonary artery via jugular veins: a 5F catheter served for determination of cardiac output by thermodilution; to facilitate rapid mixed venous blood sampling without excessive suction, a larger 7F catheter was used, which also served for pressure measurements. A pigtail catheter was advanced into the left ventricle via a common carotid artery for protamine infusion and determination of left ventricular end-diastolic pressure. Systemic and pulmonary vascular resistances were calculated from the aortic to right atrial and the pulmonary artery to left ventricular end-diastolic pressure gradients, respectively, and from cardiac output.

Laboratory Analyses

Blood gas tensions were measured using an ABL 300 (Radiometer, Copenhagen, Denmark). White blood cell counts were performed by a Coulter counter (model T 540, Coulter Electronics, Krefeld, Germany). Platelet counts were made in a counting chamber by means of a light microscope at a magnification of × 400.

Plasma levels of thromboxane B_2, the stable metabolite of thromboxane A_2, were measured by a radioimmunoassay in unextracted arterial plasma. Dextran-coated charcoal was used to separate free from antibody-bound antigen fractions. Antibodies were purchased from Pasteur Diagnostics (Paris, France).

Platelet-Activating Factor Assay

Serum concentrations of PAF were detected by a thrombocyte aggregation assay as first described by Benveniste and coworkers (9). Rabbit platelets were prepared with slight modifications according to Pinckard (10). In brief, rabbit blood was collected in ethylenediaminetetraacetic acid and centrifuged at room temperature at 500 *g* for 15 min. The platelet-rich plasma was removed, put on Ficoll 1088, and centrifuged again for 15 min at 750 *g*. The resulting platelet layer was suspended in calcium-free Tyrode's solution, pH 6.5, containing 0.1 mM ethylenediaminetetraacetic acid and 0.1 mM acetyl salicylic acid. After 10 min incubation the suspension was again placed on Ficoll 1088 and centrifuged at 750 *g* for 15 min. The washed platelets were suspended in calcium-free Tyrode's buffer, pH 6.5, at a concentration of 3×10^{12}/L and used immediately for further analyses.

For the thrombocyte aggregation assay a four-channel aggregometer (Bio/Data Corp., Hatboro, Pa.) was used. Glass vials were filled with 160 μL of Tyrode's solution, pH 7.2, containing 260 mg/L calcium and an adenosine diphosphate scavenging system (1 mM creatine phosphate and 10 U/L creatine phosphokinase). Forty microliters of the thrombocyte suspension was added and incubated for 4 min. Twenty microliters of either PAF standard (PAF dissolved in Tyrode's solution, pH 7.2, containing 0.25% bovine serum albumin) or test serum was added. Aggregation of thrombocytes was recorded as an increase of light transmission through the suspension. Specificity of aggregation for PAF was verified by adding a PAF receptor antagonist (WEB 2086, Boehringer Ingelheim, Germany).

Recovery of PAF from porcine blood was determined in vitro. Varying amounts of synthetic PAF were added to samples of normal porcine blood to provide hematocrit-corrected plasma concentrations of about 10–5000 ng/L. Blood samples were centrifuged and the plasma was processed as described above either immediately or after storage at −60°C for 1 wk.

Experimental Protocol

Baseline recordings and blood samples were obtained in all animals 30 min after surgical preparations, i.e., with stable hemodynamic conditions 15 min before protamine infusion (−15 min). All animals then received heparin (250 IU/kg) intravenously, and recordings were repeated after 5 (−10 min) and 15 (0 min) min. This was followed by infusion of 100 mg protamine over 2 min. Data were again recorded immediately (2 min) and 5 (5 min) and 15 (15 min) min after protamine infusion. The animals were randomly assigned initially to three, later to four experimental groups; the above protocol was used in all groups.

Group 1 animals ($n = 8$), the positive control for heparin-protamine effects, underwent the basic protocol without any variations. In group 2 animals ($n = 8$) the potentially protective effect of arterial injection of protamine was tested by infusing protamine into the left ventricle via the pigtail catheter. Group 3 animals ($n = 9$) were given the H_1- and H_2-antagonists clemastine (2 mg) and ranitidine (50 mg) 5 min before protamine infusion. A fourth group ($n = 5$) was introduced during the study to confirm the results of the PAF assay. These animals received the PAF receptor antagonist WEB 2086 (5 mg/kg) 5 min before protamine. Effectiveness of this dose of WEB 2086 was confirmed by injecting 40 ng/kg synthetic PAF into six pigs with ($n = 3$) or without ($n = 3$) prior treatment with the PAF antagonist.

Statistics

Results are given as mean ± SEM. The statistical significance of changes 2, 5, and 15 min after protamine administration versus the preprotamine values (0 min) was evaluated by Friedman's ranked analysis of variance and differences between groups by Kruskal–Wallis analysis. Multiple comparisons were performed according to Conover, as published for related (11) and independent (12) samples by Theodorsson-Norheim. A P-value less than 0.05 was considered statistically significant.

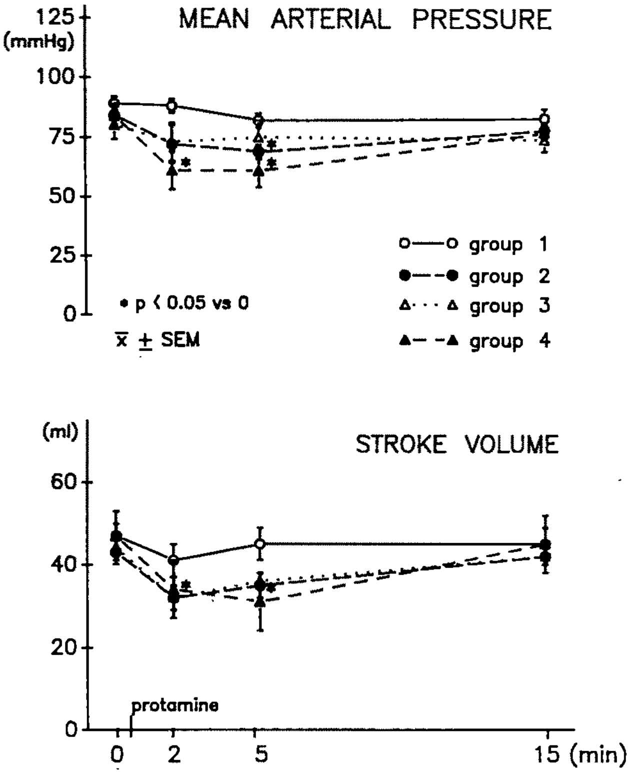

Figure 1. Mean arterial pressure and heart stroke volume in all four groups before (0) and 2, 5, and 15 min after protamine infusion. Group 1: control animals, central venous infusion of protamine; group 2: left-sided infusion of protamine, into the left ventricle; group 3: pretreatment with H_1- and H_2- receptor antagonists clemastine and ranitidine; and group 4: pretreatment with PAF receptor antagonist WEB 2086.

Results

Hemodynamic reactions, thromboxane B_2 plasma levels, and leukocyte counts after protamine infusion are summarized for all four groups in Figures 1–3.

Effects of Heparin, WEB 2086, and Clemastine/Ranitidine

In all four groups heparin alone had no effect on hemodynamic function, blood cell counts, or arterial thromboxane B_2 concentrations. Similarly, neither the PAF antagonist WEB 2086 nor the combination of the H_1- and H_2-antagonists clemastine and ranitidine had any effect on the measured variables.

Control Animals, Group 1

During right atrial protamine infusion mean pulmonary artery pressure started to increase above its

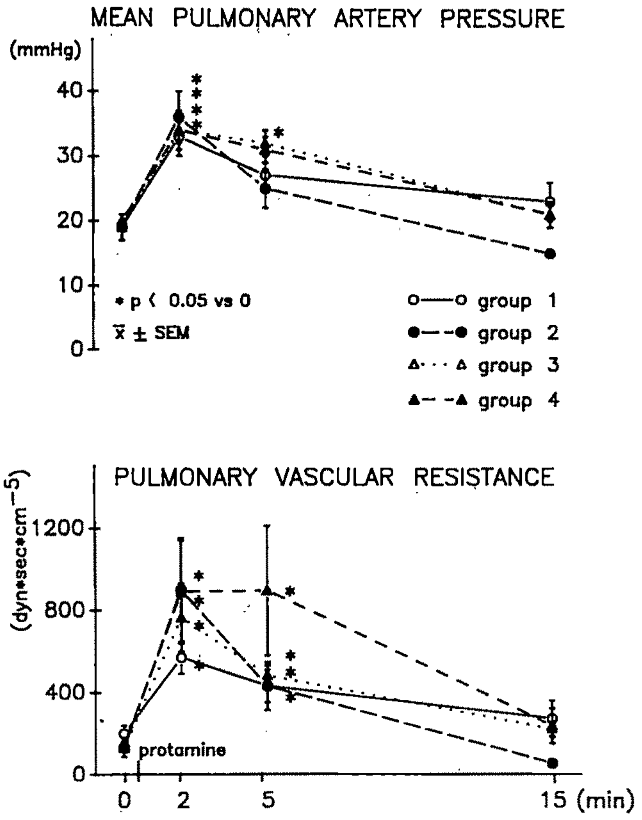

Figure 2. Mean pulmonary artery pressure and pulmonary vascular resistance in all four groups before (0) and 2, 5, and 15 min after protamine infusion. For explanation of groups, see Figure 1.

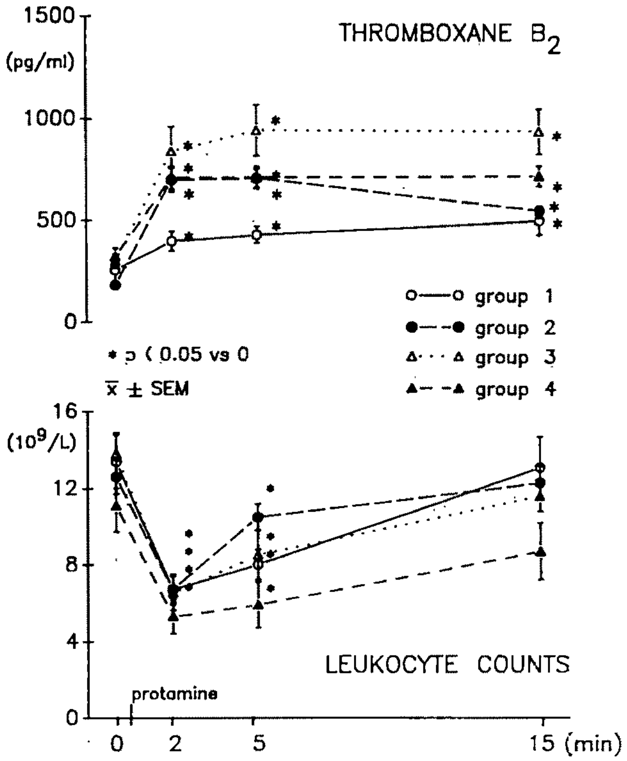

Figure 3. Thromboxane B_2 plasma concentrations and leukocyte counts in all four groups before (0) and 2, 5, and 15 min after protamine infusion. For explanation of groups, see Figure 1.

baseline value of 19 ± 2 mm Hg and averaged 33 ± 3 mm Hg at 2, 27 ± 2 at 5, and 23 ± 3 at 15 min after protamine. Values at 2 and 5 min were significantly above baseline. Pulmonary vascular resistance increased by a maximum of 185% at 2 min. Mean arterial pressure and cardiac output remained essentially unchanged, but heart rate increased slightly, by 15%. Thromboxane B_2 plasma concentrations increased 95%; leukocyte counts decreased 50% at 2 min after protamine and returned to baseline levels after 15 min. Platelet counts remained essentially unchanged.

Arterial Application of Protamine, Group 2

Infusion of protamine into the left ventricle at the same infusion rate as in control animals increased mean pulmonary artery pressure from 19 ± 2 to 36 ± 4 and 25 ± 3 mm Hg at 2 and 5 min, respectively. Pulmonary vascular resistance increased 580%. Heart rate remained essentially unchanged, while mean arterial pressure decreased slightly, by 18%, 5 min after protamine. Cardiac output and stroke volume decreased 23% and 26%, respectively. Thromboxane B_2 plasma concentration increased 287%. Leukocyte counts decreased 47% at 2 min and returned to baseline levels 15 min after protamine; platelet counts did not change significantly.

Clemastine/Ranitidine-Pretreated Animals, Group 3

In this group protamine also caused transient pulmonary hypertension with mean pulmonary artery pressure increasing from 19 ± 2 to 34 ± 3 mm Hg at 2 min and to 32 ± 2 mm Hg at 5 min after protamine infusion. Pulmonary vascular resistance increased 493%. Heart rate and systemic arterial pressure did not change significantly, but cardiac output decreased 27% 2 min after protamine infusion and returned to baseline 3 min later. Stroke volume decreased 2 and 5 min after protamine. In these animals plasma thromboxane B_2 concentration increased 214%. Maximal decreases in leukocyte counts, 53%, occurred 2 min after protamine and in platelet counts, 30%, 5 min after protamine.

Platelet-Activating Factor Assay

The minimum concentrations of synthetic PAF that caused detectable platelet aggregation depended on the quality of the platelet preparation and ranged from 10 to 50 ng/L. In none of the 52 investigated serum samples, taken from control animals as well as WEB 2086 pretreated animals before and 2, 5, and 15 min after protamine infusion, did we observe detectable platelet aggregation. Because recovery of synthetic PAF from porcine blood was 73% in the immediately processed plasma samples and 55% in the frozen and rethawed plasma, serum PAF concentrations were consistently below 20–100 ng/L in all animals and did not increase beyond this concentration during the heparin-protamine reaction.

Effectivity of WEB 2086

In the three untreated animals 40 ng/kg synthetic PAF caused severe pulmonary hypertension and systemic hypotension; this resulted in death by cardiac arrest in one pig. Injection of 5 mg/kg WEB 2086 5 min before PAF prevented these effects.

WEB 2086-Pretreated Animals, Group 4

In animals pretreated with PAF receptor antagonist protamine infusion increased mean pulmonary artery pressure from 20 ± 1 to 34 ± 2 and 32 ± 2 mm Hg within 2 and 5 min, respectively. Maximal increase in pulmonary vascular resistance, 545%, occurred at 2 min. Heart rate remained unchanged, but mean arterial pressure decreased 27% and returned to baseline levels after 15 min. Decreases in cardiac output and stroke volume, although amounting to 28% and 33%, respectively, were statistically not significant. The increase in thromboxane B_2 concentration amounted to 123%. The maximal decrease of leukocyte counts was 52% at 2 min and of platelet counts 25% at 5 min after protamine infusion.

Statistical Comparisons Between Groups

With few exceptions, reactions to protamine reversal of heparin were not different among the four experimental groups. Cardiac output decreased significantly more in group 2 at 2 min after left ventricular infusion of protamine as compared with control animals, where protamine was infused into the right atrium. Also, in group 2 animals leukocyte counts 5 min after protamine were higher than in the other three groups. Platelet counts decreased more in group 3 (clemastine/ranitidine) and in group 4 (WEB 2086) than in group 1 (control) animals.

Discussion

The results of this study indicate (a) arterial infusion of protamine for reversal of heparin does not influence the severity of pulmonary vasoconstriction; and (b) histamine and PAF are not involved in pulmonary vasoconstriction after heparin-protamine.

In the present study an anesthetized pig model and experimental protocol were used that had proven useful in previous studies of heparin-protamine reactions (6,7). In all animals 100 mg protamine was slightly in excess of the amount required for reversal of the 250 IU/kg heparin injected 17–18 min previously. Thus, using a fixed dose of protamine to antagonize a variate dose of heparin should have only a minor effect on the results. Although not common in clinical practice, protamine was infused over 2 min because this infusion rate has reproducibly produced severe pulmonary hypertension in pigs (6,7).

The effects of heparin-protamine on hemodynamics, thromboxane A_2 release, and blood cell counts in this study correlate well with previously published results from this laboratory (6,7) as well as with observations in other animal species (5,13) and in humans (3,14). The most severe reaction to protamine infusion was transient pulmonary vasoconstriction, with pronounced increases of pulmonary artery pressure and pulmonary vascular resistance, often, but not necessarily, accompanied by decreases in left ventricular filling pressure, cardiac output, and mean arterial pressure. These hemodynamic effects occurred together with an increase in thromboxane B_2 plasma concentrations, a transient decrease of leukocyte counts, and, in some studies, a less pronounced decrease in platelet counts. Usually all variables return to normal within a short period, about 15 min in the present study. This pattern represents the type III reaction, catastrophic pulmonary vasoconstriction, according to the classification of adverse protamine reactions in two recent review articles by Horrow (1,2). This type of reaction is observed infrequently in humans, but it occurs regularly in the present pig model or in sheep (5). Type I (systemic hypotension related to rapid administration) and type II (anaphylactic or anaphylactoid) reactions are obviously not involved or are masked by catastrophic pulmonary vasoconstriction in the pig model. Therefore, discussion of results of this study will refer to the type III reaction only, and conclusions concerning possibly protective effects of the investigated receptor blockers in type I or type II reactions after protamine reversal of heparin cannot be drawn.

The rationale for comparing the effects of arterial and venous infusion of protamine was the hypothesis that release of vasoactive substances from the lung might be reduced when protamine was diluted or already complexed with heparin before reaching the pulmonary vasculature (15). Several animal studies comparing left- and right-sided injections of protamine have been inconclusive (2). A study performed in pigs provided no difference in hemodynamic reactions after intraaortic or intravenous infusion of protamine, but thromboxane release and blood cell counts were not measured in these animals (16). A number of studies in humans found no advantage for arterial versus venous infusion of protamine insofar as changes in systemic blood pressure were concerned (17–19), but pulmonary artery pressure did not increase in these patients; therefore, effects on pulmonary hypertension could not be detected.

The results of the present study clearly indicate that arterial infusion of protamine provides no protection against catastrophic pulmonary vasoconstriction as compared with venous infusion. On the contrary, the decrease of cardiac output was even significantly more pronounced in group 2 when protamine was infused into the left ventricle than in group 1 with central venous infusion of protamine. Also, the initial decrease of leukocyte counts was identical after arterial and venous infusion of protamine. The relevance of significantly less depressed leukocyte counts in group 2 at 5 min after protamine is unclear.

As early as 1949 Jaques claimed there was a causal connection between the hemodynamic reactions and the activation of platelets after heparin-protamine. In dogs, the pronounced decrease in blood pressure was associated with a decrease in platelet counts, and experimentally induced thrombopenia before the infusion of protamine prevented the decrease in blood pressure (20). In patients, the administration of protamine is uniformly associated with a decrease in platelet counts (3,4,14). Acetylsalicylic acid or indomethacin prevents pulmonary vasoconstriction but not thrombopenia after protamine infusion in dogs and in pigs (7,21), suggesting that cyclooxygenase metabolites of arachidonic acid induce the vascular reactions to protamine but not thrombopenia. The observation that thromboxane A_2 largely mediates the hemodynamic effects of heparin-protamine (5,7) might support the hypothesis of a causal contribution of activated platelets to this reaction.

The manner in which platelets are activated by heparin-protamine, however, remains unclear. We studied the hypothesis that PAF was involved in the activation of platelets and the pulmonary vasoconstriction after heparin-protamine.

The effects of PAF have been investigated in several animal and in vitro models (8). Decreases in platelet and leukocyte counts, systemic hypotension, and pulmonary hypertension, as well as the release of thromboxane and prostacyclin, fit well into the pattern of effects observed after heparin-protamine. The finding that PAF can induce pulmonary hypertension and thromboxane release even in cell-free perfused lungs (22) indicates that, although platelets themselves may not be necessary for the pulmonary effects of heparin-protamine (23), PAF might still be involved by a direct action on the pulmonary endothelium.

Possible sources of PAF production could be platelets, stimulated leukocytes, or endothelial cells (8). Regarding the widely described complement activation by heparin-protamine interaction in vitro (24), in animals (5), and in humans (4,25), the release of PAF from mast cells, responding to C_{5a} formation (26), could have been a pathway involved in the mediator sequence finally resulting in thromboxane release and the hemodynamic effects of heparin-protamine.

However, the data of the present study disprove the existence of a causal participation of PAF in the heparin-protamine reaction. The PAF bioassay employed in this study has been successfully used to detect PAF generation in vivo (10). In our laboratory, detectable platelet aggregation was achieved with PAF standards at concentrations as low as 10–50 ng/L. Recovery of PAF from porcine blood was studied because rapid metabolization of PAF has been described in vivo (8) and might also occur during the processing of the blood samples. The reduced recovery of synthetic PAF from porcine blood elevates the actual detection limit to 20–100 ng/L. The assay was highly specific for PAF because platelet aggregation could be totally prevented by adding the PAF receptor antagonist WEB 2086 to the platelet suspension. Thus, the finding in this study that PAF was not detected in any of the serum samples before or after heparin-protamine administration is highly reliable in that PAF in detectable amounts was not present in the serum samples.

This does not, however, totally exclude a role of PAF in the heparin-protamine reaction, because concentrations of PAF even lower than 20 ng/L might be biologically active. Therefore, five animals were studied in which PAF was antagonized by 5 mg/kg WEB 2086 5 min before protamine infusion. In the preliminary experiments, this dosage had proven effective in completely suppressing the hemodynamic effects of injected synthetic PAF. Because WEB 2086 did not prevent or even modulate the hemodynamic reactions, thromboxane release, or the decrease in leukocyte counts after heparin-protamine, a causal role of PAF as mediator of the heparin-protamine reaction can be excluded. Thus, use of PAF antagonists cannot be expected to reduce the incidence or severity of adverse type III reactions to heparin-protamine.

A vasoactive agent that has long been studied as a major factor in heparin-protamine reactions is histamine (20,27). The hypotensive effect of protamine in dogs has been described as histamine-like, and in volunteers protamine has produced typical symptoms of histamine release such as itching, flushing, fatigue, nausea, headache, hyperventilation, and temperature elevation (27). Also, in vitro, organic cations like polyarginine or polylysine induced histamine secretion from human basophil leukocytes (28). Surprisingly, in the same study protamine, a cationic polypeptide containing 66% arginine, failed to release histamine. However, a later study showed that protamine potentiated the immunoglobulin E-stimulated histamine release from human basophils (29), thus confirming a possible role of histamine in protamine reactions. In patients, a decrease in systemic pressure after protamine reversal of heparin after cardiopulmonary bypass was accompanied by increased histamine plasma levels (30). Also, histamine receptor blockade attenuated the protamine-induced systemic hypotension in patients after cardiopulmonary bypass (31).

Thus, the finding in group 3 animals of the present study that simultaneous H_1- and H_2-blockade had no effect on hemodymic changes, thromboxane release, or leukocyte counts in the heparin-protamine reaction appears to conflict with these previous reports. However, the histaminelike effects in dogs and human volunteers occurred after protamine injection without prior heparinization, whereas in pigs (7) and sheep (5) protamine alone had no or only negligible hemodynamic effects. It seems likely that different types of protamine reactions as defined by Horrow (1) account for the different findings in these studies. Also, in studies in humans in which histamine release was detected (30) or histamine antagonists proved effective (31), type I reactions, i.e., systemic hypotension after rapid injection of protamine rather than catastrophic pulmonary vasoconstriction of type III reaction, were investigated. Fortunately, type III reactions occur only infrequently in humans although observed regularly in sheep and pigs, which, therefore, have been chosen for investigating its mechanisms (5–7). Histamine levels were not measured in the present study. However, because histamine antagonists were ineffective in the present animal model of catastrophic pulmonary vasoconstriction, a possible finding of elevated histamine concentrations would not suggest an actual role of histamine in the type III reaction. It would rather be due to a simultaneously occurring mild type I reaction, which is masked by the predominant pulmonary vasoconstriction. Thus, the data of the present study do not contradict previous findings of a possible role of histamine in type I reactions, but clearly exclude a major role of histamine in pulmonary hypertension after heparin-protamine.

Although the findings of the present study do not provide a conclusive explanation for the mechanisms responsible for the thromboxane A_2 release that causes acute pulmonary hypertension in heparin-protamine reactions, they clearly show that neither histamine nor PAF are involved in this reaction. Because the mechanisms that are active in the heparin-protamine reaction might represent a pathophysiological principle that acts in other reactions as well, further studies are desirable to identify all steps of the mediator sequence that finally results in thromboxane A_2 release and its adverse hemodynamic effects.

The authors gratefully acknowledge the technical skill of Anne Holzer and Sylvia Schneider, and thank Boehringer Ingelheim KG, 6507 Ingelheim am Rhein, Germany, for generously supplying the PAF antagonist WEB 2086.

References

1. Horrow JC. Protamine: a review of its toxicity. Anesth Analg 1985;64:348–61.
2. Horrow JC. Protamine allergy. J Cardiothorac Anesth 1988;2: 225–42.
3. Lowenstein E, Johnston WE, Lappas DG, et al. Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 1983;59:470–3.
4. Morel DR, Zapol WM, Thomas SJ, et al. C5a and thromboxane generation associated with pulmonary vaso- and bronchoconstriction during protamine reversal of heparin. Anesthesiology 1987;66:597–604.
5. Morel RD, Lowenstein E, Nguyenduy T, et al. Acute pulmonary vasoconstriction and thromboxane release during protamine reversal of heparin anticoagulation in awake sheep. Circ Res 1988;62:905–15.
6. Hobbhahn J, Cozen PF, Zenker B, Goetz AE, Peter K, Brendel W. Beneficial effect of cyclooxygenase inhibition on adverse hemodynamic responses after protamine. Anesth Analg 1988; 67:253–60.
7. Conzen PF, Habazettl H, Gutmann R, et al. Thromboxane mediation of pulmonary hemodynamic responses after neu-

tralization of heparin by protamine in pigs. Anesth Analg 1989;68:25–31.

8. Braquet P, Touqui L, Shen Y, Vargaftig BB. Perspectives in platelet-activating factor research. Pharmacol Rev 1987;39:97–145.
9. Benveniste J, Henson PM, Cochrane CG. Leukocyte-dependent histamine release from rabbit platelets: the role of IgE, basophils, and a platelet-activating factor. J Exp Med 1972;136:1356–77.
10. Pinckard RN, Farr RN, Hanahan DJ. Physiochemical and functional identity of rabbit platelet activating factor (PAF) released during IgE anaphylaxis with PAF released in vitro from IgE sensitized basophils. J Immunol 1979;123:1847–57.
11. Theodorsson-Norheim E. Friedman and Quade tests: BASIC computer program to perform nonparametric two way analysis of variance and multiple comparisons on ranks of several related samples. Comput Biol Med 1987;17:85–99.
12. Theodorsson-Norheim E. Kruskal Wallis test: BASIC computer program to perform nonparametric one way analysis of variance and multiple comparisons on ranks of several independent samples. Comput Meth Progr Biomed 1986;23:57–62.
13. Stefanyszin HJ, Novick RJ, Salerno TA. Toward a better understanding of the hemodynamic effects of protamine and heparin interaction. J Thorac Cardiovasc Surg 1984;87:678–86.
14. Hobbhahn J, Conzen P, Habazettl H, et al. Precipitous decrease in leukocyte and platelet counts and prostaglandin release after heparin reversal by protamine in humans. Anesthesiology 1988;69:A118.
15. Goldman BS, Joison J, Austen WG. Cardiovascular effects of protamine sulfate. Ann Thorac Surg 1969;7:459–71.
16. Rogers K, Milne B, Salerno TA. The hemodynamic effects of intra-aortic versus intravenous administration of protamine for reversal of heparin in pigs. J Thorac Cardiovasc Surg 1983;85:851–5.
17. Cherry DA, Chiu RCJ, Wynands JE, et al. Intra-aortic vs intravenous administration of protamine: a prospective randomized clinical study. Surg Forum 1985;36:238–40.
18. Milne G, Rogers K, Cervenko F, Salerno T. The haemodynamic effects of intraaortic versus intravenous administration of protamine for reversal of heparin in man. Can Anaesth Soc J 1983;30:347–51.
19. Pauca AL, Graham JE, Hudspeth AS. Hemodynamic effects of intraaortic administration of protamine. Ann Thorac Surg 1983;35:637–42.
20. Jaques LB. A study of the toxicity of the protamine, salmine. Br J Pharmacol 1949;4:135–44.
21. Radegran K, McAslan C. Circulatory and ventilatory effects of induced platelet aggregation and their inhibition by acetylsalicylic acid. Acta Anaesthesiol Scand 1972;16:76–84.
22. Lefort J, Rotilio D, Vargaftig BB. The platelet-independent release of thromboxane A_2 by PAF-acether from guinea pig lungs involves mechanisms distinct from those of leukotrienes. Br J Pharmacol 1984;82:565–75.
23. Montallescot G, Kreil E, Lynch K, et al. Effect of platelet depletion on lung vasoconstriction in heparin-protamine reactions. J Appl Physiol 1989;66:2344–50.
24. Rent R, Ertel N, Eisenstein R, Gewurz H. Complement activation by interaction of polyanions and polycations. I. Heparin-protamine induced consumption of complement. J Immunol 1975;114:120–4.
25. Cavarochi NC, Schaff HV, Orszulak TA. Evidence for complement activation by protamine-heparin interaction after cardiopulmonary bypass. Surgery 1985;98:525–30.
26. Camussi G, Mencia-Huerta JM. Release of platelet activating factor and histamine. I. Effect of immune complexes, complement and neutrophils on human and rabbit mastocytes and basophils. Immunology 1977;33:523–34.
27. Jaques LB, Saskatoon S. Protamine—antagonist to heparin. J Can Med Assoc J 1973;108:1291–7.
28. Foreman JC, Lichtenstein LM. Induction of histamine secretion by polycations. Biochim Biophys Acta 1980;629:587–603.
29. Tobin MC, Karns BK, Anselmino LM, Thomas LL. Potentiation of human basophil histamine release by protamine: a new role for a polycation recognition site. Mol Immunol 1986;23:245–53.
30. Frater RWM, Oka Y, Hong Y, Tsubo T, Loubser PG, Masone R. Protamine-induced circulatory changes. J Thorac Cardiovasc Surg 1984;87:687–92.
31. Parsons RS, Mohandas K. The effect of histamine-receptor blockade on the hemodynamic responses to protamine. J Cardiothorac Anesth 1989;3:37–43.

Comparison of Midazolam and Propofol in Combination With Alfentanil for Total Intravenous Anesthesia

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VUYK J, HENNIS PJ, BURM AGL, DE VOOGT JWH, SPIERDIJK J. Comparison of midazolam and propofol in combination with alfentanil for total intravenous anesthesia. Anesth Analg 1990;71:645–50.

Hemodynamic function during induction of anesthesia, the alfentanil and naloxone requirements, and the speed of recovery from total intravenous anesthesia with alfentanil/midazolam (group M, $n = 10$) or alfentanil/propofol (group P, $n = 10$) were compared in patients undergoing lower limb surgery. Twenty patients were randomly assigned to receive either 2 mg/kg propofol in 5 min followed by 9 $mg\cdot kg^{-1}\cdot h^{-1}$ for 30 min and 4.5 $mg\cdot kg^{-1}\cdot h^{-1}$ until skin closure, or 0.42 mg/kg midazolam in 5 min followed by 0.125 $mg\cdot kg^{-1}\cdot h^{-1}$ until skin closure. Simultaneously, a variable-rate infusion of alfentanil was given. Patients were ventilated with 30% oxygen in air. In both groups blood pressure and heart rate decreased significantly ($P < 0.02$) and to a similar extent during induction. The total dose of alfentanil was similar in both groups. No patient in group P and nine patients in group M needed naloxone (average dose 130 ± 70 μg, $P < 0.001$). Recovery, as judged by psychomotor tests (90% score was reached at 1 h in the P group and at about 4 h in the M group, $P < 0.001$), sedative scores, and orientation in time and place, was shorter in group P than in group M. The conclusion is reached that propofol is superior to midazolam in total intravenous anesthesia with alfentanil.

Key Words: ANESTHETICS, INTRAVENOUS—midazolam, propofol. ANESTHETIC TECHNIQUES, INTRAVENOUS—total. ANALGESICS, ALFENTANIL.

The introduction of short-acting noncumulative intravenous (IV) anesthetics has increased the controllability and thus the interest in total intravenous anesthesia (TIVA). Total intravenous anesthesia has advantages compared with anesthesia with nitrous oxide or volatile anesthetics. For example, TIVA avoids operating room pollution with trace amounts of gaseous and volatile anesthetics and, because no nitrous oxide is used, is likely to reduce the incidence of intraoperative and postoperative hypoxia. On the other hand, TIVA has disadvantages as well. During TIVA, hypnosis and analgesia are induced and maintained separately by different agents. Consequently, to control anesthetic depth properly one has to be able to distinguish whether a patient shows signs of inadequate hypnosis or suffers from pain. Because at this moment no parameter is available for accurately measuring the intraoperative depth of hypnosis, hypnotic agents are infused according to standard infusion schemes causing some patients to be barely asleep and others to be overdosed.

Hypnotic agents differ remarkably in their pharmacologic profile. Among their differences are those in hemodynamic effects, speed of recovery, and occurrence of anterograde amnesia. Both midazolam (1) and propofol (2) have been clinically evaluated and are suitable for continuous infusion because of their relatively short elimination half-lives. Although it is claimed that propofol results in very rapid recovery, comparative studies with midazolam in TIVA are lacking. In this study we compared the hemodynamics of induction, the alfentanil and naloxone requirements, and the speed of recovery of these two hypnotic agents in combination with alfentanil for TIVA.

Supported in part by the Ministry of Defence, The Hague, and ICI-Farma, Rotterdam, the Netherlands.

Presented in part at the Second Open Annual Meeting of the European Academy of Anaesthesiology in Mainz, Germany.

Received from the Department of Anesthesiology, Leiden University Hospital, Leiden, the Netherlands. Accepted for publication August 6, 1990.

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Patients and Methods

After obtaining informed consent and approval by the Medical Ethics Committee, 20 ASA physical status I patients with an age range of 18–45 yr who were scheduled for lower limb surgery were studied. Patients with a history of hepatic or renal disease, and patients using sedatives or drinking more than two alcoholic beverages a day, were excluded from the study. The patients were randomly assigned to one of two study groups, receiving either midazolam (group M) or propofol (group P) in combination with alfentanil.

Premedication was with 10 mg oral temazepam 1 h preoperatively. On the patient's arrival in the operation room, electrocardiogram electrodes were placed on the chest and blood pressure was measured. A nerve stimulator (Myotest) was installed by fixing two electrodes on the ulnar side of the wrist, and an intravenous cannula was placed in a large forearm vein.

After 3 min of preoxygenation, anesthesia was induced and then maintained by infusion of either midazolam or propofol, and alfentanil. Propofol infusion was started with a loading dose of 2 mg/kg in 5 min, followed by a continuous infusion of 9 $mg \cdot kg^{-1} \cdot h^{-1}$ for 30 min and then 4.5 $mg \cdot kg^{-1} \cdot h^{-1}$ until skin closure (3). Midazolam infusion was started with a loading dose of 0.42 mg/kg in 5 min, followed by a continuous infusion of 0.125 $mg \cdot kg^{-1} \cdot h^{-1}$ until skin closure (4). At the time of starting the infusion of midazolam or propofol, a bolus of 25 μg/kg alfentanil was given and the infusion rate of alfentanil was started at 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$. An additional 25 μg/kg alfentanil was given just before skin incision. No preload was given. During induction 150–200 mL of 2.5% glucose/0.9% NaCl was infused. As soon as the patients were unconscious, 0.1 mg/kg vecuronium was given and the trachea was intubated. Ventilation was maintained with 30% oxygen in air to an end-tidal carbon dioxide concentration of 4–5 vol% for the entire procedure.

Alfentanil administration was continued by variable-rate infusion (5). When signs of inadequate anesthesia developed, an additional bolus of 7 μg/kg was given and the infusion rate increased by 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ to a maximum of 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$. After a 15-min absence of such signs the infusion rate was decreased by 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ to a minimum of 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Inadequate anesthesia was defined by the following criteria:

1. An increase in systolic blood pressure by more than 15 mm Hg above normal for that patient. The normal systolic blood pressure was defined as the mean of three systolic blood pressures measured from admission until premedication.
2. A heart rate exceeding 90 beats/min in the absence of hypovolemia.
3. Other autonomic signs such as sweating or flushing.
4. Somatic responses such as movements, swallowing, or eye movements.

The alfentanil infusion was stopped 10 min before skin closure. Neuromuscular transmission was monitored every 5–15 min by percutaneous stimulation of the ulnar nerve using the "train-of-four" method. After the reappearance of the fourth twitch, an additional 1 mg IV vecuronium was given. After skin closure, residual neuromuscular blockade was antagonized by 1 mg IV neostigmine and 0.5 mg IV atropine. If end-tidal carbon dioxide concentration was less than 6 vol%, tidal volume more than 7 mL/kg, and respiratory rate more than 10 breaths/min, the trachea was extubated. If, 10 min after skin closure, patients did not breathe adequately, respiratory depression was antagonized by 40 μg IV naloxone every 2 min. After extubation the patient was transported to the recovery room. Approximately 1.5 h later the patient was returned to the ward.

Blood pressure and heart rate were measured before induction, every minute during induction, and every 5 min throughout the rest of the procedure. The means of three measurements before induction, three measurements before intubation, and three measurements after intubation were compared. The induction time, defined as the time from the start of midazolam or propofol infusion to loss of verbal contact and eyelash reflex, was recorded. The same was done for the recovery time, i.e., the time from termination of the midazolam or propofol infusion until extubation. To evaluate further the speed of recovery, patients were asked to perform two psychomotor tests (6,7): the "blocks" test and the "deletion of *p*'s" test, preoperatively and 5, 30, 60, 120, and 240 min postoperatively. In the blocks test, patients were asked to put in 20 s as many blocks as possible through four corresponding holes in a wooden board. In the deletion of *p*'s test, patients were asked to delete in 2 min as many *p*'s as possible on a foolscap sheet of closely packed, randomly typed, letters. Only correctly deleted *p*'s were counted. At the same time the degree of sedation was scored using a four-point scale (1, awake; 2, drowsy; 3, asleep but arousable; 4, asleep, not arousable); orientation in time and place was scored on a three-point scale (0, none; 1, orientation in either place or time; 2, orientation in both). On the day after the operation, the patients were interviewed to evaluate possible side effects and to assess the duration of anterograde amnesia by asking them to recall their first conscious moments postoperatively and the number of tests they had done the day before.

Statistical Analysis

Patient data, induction times, duration of anesthesia, and total drug doses were tested for normality with the Shapiro–Wilk test and compared between the M and P groups with the unpaired Student's t-test or Mann–Whitney U-test, where appropriate. The Fisher exact test was used to compare proportions. Hemodynamic data were analyzed by repeated-measures analysis of variance and paired t-tests. The postoperative time-course in the performance of the deletion of p's test and the blocks test was evaluated for each patient by linear regression over the appropriate time intervals. The times from arrival in the recovery room until the patients scored 50% and 90% of their preoperative values were estimated for each patient and compared between the two groups with the Mann–Whitney U-test. $P < 0.05$ was considered as the minimum level of statistical significance, except for multiple (triple) comparison tests, where $P < 0.02$ was considered significant. Data are presented as mean ± SD, or as proportions, where appropriate.

Results

Patients in the two groups were comparable with respect to age, weight, sex distribution, and types of surgery (Table 1). The mean propofol dose was 856 ± 285 mg, infused in 96 ± 44 min. The mean midazolam dose was 46 ± 13 mg, infused in 97 ± 56 min. The induction time was similar in both groups (2.9 ± 1.0 min in group P and 2.0 ± 0.8 min in group M). In both groups, systolic and diastolic blood pressures and heart rate decreased significantly after induction ($P < 0.02$) and remained lower than the preinduction values after intubation (Table 2). No significant difference was found in systolic or diastolic blood pressure or in heart rate over time between the two groups.

Table 1. Patient Data and Type of Surgery

M group				P group			
n	Sex	Age (yr)	Weight (kg)	*n*	Sex	Age (yr)	Weight (kg)
1[a]	F	31	50	2[a]	M	23	87
5[a]	M	44	81	3[a]	M	30	99
8[b]	M	27	73	4[a]	M	27	98
10[b]	M	25	82	6[b]	M	23	67
11[c]	M	23	85	7[c]	F	33	54
13[b]	M	22	72	9[c]	M	38	77
14[c]	M	44	72	12[a]	M	23	85
17[b]	M	26	73	15[c]	M	18	60
19[c]	M	38	85	16[b]	M	31	87
20[c]	M	19	85	18[a]	M	24	63
Mean		30	75			27	78
SD		9	10			6	16

The M group was given alfentanil/midazolam; the P group was given alfentanil/propofol. See text for details.

[a] Osteosynthesis.

[b] Extraction of osteosynthetic material.

[c] Arthroscopy of the knee.

Table 2. Systolic and Diastolic Blood Pressures and Heart Rate Before Induction, After Induction, and After Intubation

	M group	P group[a]
Systolic blood pressure (mm Hg)		
Before induction	127.3 ± 13.1	128.4 ± 14.6
After induction	105.2 ± 12.2[b]	101.1 ± 11.8[b]
After intubation	112.8 ± 10.9[b]	101.8 ± 11.2[b]
Diastolic blood pressure (mm Hg)		
Before induction	75.6 ± 8.5	77.2 ± 9.0
After induction	57.7 ± 7.7[b]	51.7 ± 9.0[b]
After intubation	61.6 ± 8.6[b]	53.3 ± 12.6[b]
Heart rate (beats/min)		
Before induction	69.5 ± 9.6	76.5 ± 7.8
After induction	57.8 ± 6.4[b]	58.5 ± 5.6[b]
After intubation	61.3 ± 7.4[b]	63.3 ± 9.6[b]

The M group was given alfentanil/midazolam; the P group was given alfentanil/propofol. See text for details.

[a] No significant difference was found in systolic or diastolic blood pressure or heart rate over time between groups M and P.

[b] Significantly different ($P < 0.02$) compared with values before induction.

Twelve patients showed one to eight responses indicating inadequate anesthesia. These responses could easily be controlled by a bolus of alfentanil and an increase of the infusion rate of alfentanil. Eight patients, five in the P group and three in the M group, showed no signs of inadequate anesthesia at all, even with the lowest alfentanil infusion rate of 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$. One patient in the M group continued to show signs of inadequate anesthesia while receiving the maximum alfentanil infusion rate of 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Halothane had to be administered to this patient, and therefore this patient was excluded from the study. After exclusion of this patient, the total alfentanil dose and the duration of alfentanil infusion were similar in both groups (Table 3). Nevertheless, a significant difference was found in the

Table 3. Alfentanil and Naloxone Requirements

	M group	P group	P
Alfentanil[a]			
Total dose (mg)	12.6 ± 7.6	10.0 ± 4.3	NS
Infusion time (min)	91 ± 52	89 ± 45	NS
Infusion rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	68 ± 20	52 ± 16	NS
Patients requiring naloxone (n)	9	0	<0.001

NS, not significant.
M and P groups as in Tables 1 and 2.
[a]Values are expressed as mean ± SD, except that for "Patients requiring naloxone."

Table 4. Recovery Times and Times to 50% and 90% Scores in the Deletion of *p*'s and the Blocks Tests

	M group	P group	P
Recovery time (min)[a]	16.9 ± 5.2	8.5 ± 4.6	<0.05
Blocks test			
Time to 50% score (min)[b]	115 ± 32	17 ± 11	<0.001
Time to 90% score (min)[b]	215 ± 37	78 ± 37	<0.001
Deletion of *p*'s test			
Time to 50% score (min)	141 ± 33	27 ± 6	<0.001
Time to 90% score (min)	245 ± 36	56 ± 9	<0.001

M and P groups as in Tables 1 and 2.
Values are mean ± SD.
[a]Time from stopping the infusion of midazolam or propofol until extubation.
[b]Estimated time postoperatively when patients scored 50% and 90% of their preoperative values.

naloxone requirement (Table 3). None of the patients in the P group and 9 of 10 in the M group needed naloxone to assure adequate respiration according to the described criteria ($P < 0.001$). The mean naloxone dose used in the M group was 130 ± 70 μg. It was striking that in the P group the patients did not breathe at all until regaining consciousness. As soon as they opened their eyes, adequate respiration was restored and they all could be extubated immediately. At this time, when patients in the P group regained consciousness, the patients in the M group were still heavily sedated. A significant difference was found in recovery time from termination of the infusion of the hypnotic agent until extubation (8.5 ± 4.6 min in the P group and 16.9 ± 5.2 min in the M group [$P < 0.05$, Table 4]). The mean values as scored by the patients in the two psychomotor tests display a substantial difference in recovery between the two groups (Figures 1 and 2). The times from entering the recovery room until patients scored 50% and 90% of the preoperative control values in the blocks and deletion of *p*'s tests were significantly shorter in the P group than in the M group ($P < 0.001$, Table 4). The sedation scores showed that 1 h postoperatively all

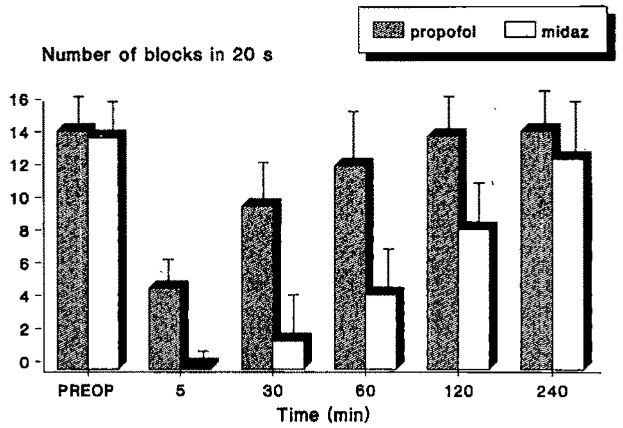

Figure 1. Mean scores in the blocks test as scored preoperatively (PREOP) and 5, 30, 60, 120, and 240 min postoperatively by the patients of both groups. *Bars* indicate standard deviations.

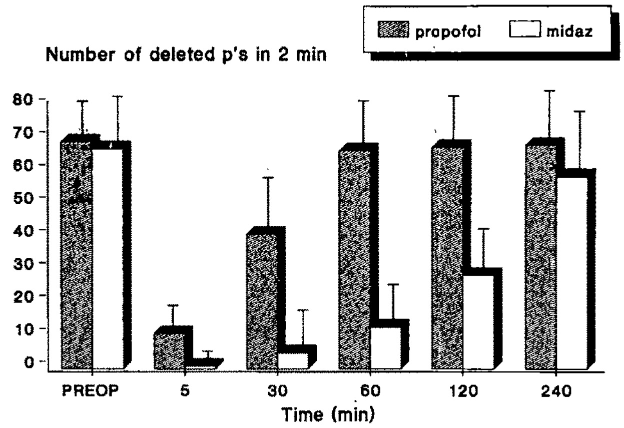

Figure 2. Mean scores in the deletion of *p*'s test as scored preoperatively (PREOP) and 5, 30, 60, 120, and 240 min postoperatively by the patients of both groups. *Bars* indicate standard deviations.

patients in the P group and none of the patients in the M group were awake (score = 1, $P < 0.001$). After 4 h, 7 of 10 patients in the M group were awake; the other three patients were still drowsy (score of 2). All patients in the P group were oriented in both time and place within 5 min after entering the recovery room, whereas this took patients in the M group 30–60 min.

All patients given propofol remembered entering the recovery room and recalled having done the psychomotor tests five times postoperatively. The patients in the M group remembered having done these tests once or twice (at 120 and 240 min postoperatively) and only remembered lying in bed in the ward postoperatively. None of the patients experienced pain on injection or nausea, and none vomited or showed signs of thrombophlebitis.

Discussion

The main objectives of this study were to compare the hemodynamics of induction, the alfentanil and naloxone requirements, and the speed of recovery from total intravenous anesthesia with alfentanil/midazolam and alfentanil/propofol. Infusion schemes were chosen such that adequate intraoperative hypnosis was assured and unnecessary overdosing was avoided. The midazolam infusion scheme was based on observations of Persson et al. (4); its goal was to obtain adequate intraoperative plasma concentrations of midazolam in the order of 300 ng/mL. A pilot study, preceding the present study, further demonstrated that adequate anesthesia was assured with a loading dose of 0.42 mg/kg midazolam, whereas with 0.25 mg/kg anesthesia was inadequate. Based on a study by Fragen et al. (3), the propofol infusion scheme was aimed at a plasma concentration of propofol in the order of 3 μg/mL, which is generally considered to be an adequate level of propofol during anesthesia.

Propofol is known to decrease systolic blood pressure by 20%–30% during induction (8–11). Grounds et al. (9) compared the hemodynamic changes after induction with 2.5 mg/kg propofol to that with 4 mg/kg thiopentone. They concluded that propofol is more cardiodepressant than thiopentone. Lebowitz et al. (12) compared the cardiovascular effects of induction with 0.25 mg/kg midazolam to those with 4 mg/kg thiopentone. They concluded that, although midazolam was associated with more gradual and less pronounced hemodynamic alterations, no significant difference could be found compared with thiopentone. Combining the results of these studies (8–13), one might conclude that 2.5 mg/kg propofol causes more profound hemodynamic changes as compared with 0.25 mg/kg midazolam. We found no significant difference in hemodynamic effects during induction with midazolam (0.42 mg/kg) as compared with propofol (2 mg/kg). Therefore we conclude that with the doses used in this study, and in combination with alfentanil, midazolam has no advantages over propofol from a hemodynamic point of view.

Intraoperative alfentanil dose requirements were similar with propofol and midazolam. The mean alfentanil dose requirements in both groups may be slightly overestimated, because five patients in the P group and three patients in the M group showed no signs of inadequate anesthesia at all. In contrast, Ausems et al. (5), using a variable-rate infusion of alfentanil in combination with nitrous oxide, described responses in all patients. The differences in the observations of this study and the study of Ausems may be related to differences in the type of surgery. Another explanation may be that the alfentanil requirement is lower during TIVA with propofol or midazolam than during anesthesia with nitrous oxide in oxygen.

The difference in naloxone requirement between the two groups, after similar dosages of alfentanil, may be explained by the difference in the pharmacokinetic profile of midazolam as compared with propofol. Propofol concentrations decline rapidly after termination of the infusion because of continued extensive distribution, in addition to elimination. Midazolam concentrations, on the other hand, decline at a slower rate, because distribution after prolonged infusion is less extensive. The combination of alfentanil with relatively high concentrations of midazolam, which in itself has respiratory depressant properties, may be partially responsible for the respiratory depression in group M. Second, our observations in group P suggest that consciousness and perception of one's environment are important stimuli in regaining adequate respiration. Because patients of group M were still heavily sedated postoperatively, they lacked the sensory input that could stimulate them to breathe adequately.

The difference in speed of recovery between the P and the M group, as measured by the deletion of *p*'s and the blocks test as well as by the sedation scores and the orientation in time and place scores, was highly significant and may be related to a difference in plasma concentration decline of the two hypnotic agents.

In summary, we conclude that, although both midazolam and propofol assured satisfactory surgical conditions in combination with alfentanil, propofol resulted in a faster recovery with less respiratory depression. Midazolam does not have an advantage from a hemodynamic point of view over propofol during induction of anesthesia. Consequently, propofol seems to be the drug of choice for TIVA in combination with alfentanil.

The authors thank M.P.M. Toelen, M.J.F. van der Keur, and J. I. Tieleman-Shamier for their secretarial assistance.

References

1. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62:310–24.
2. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. Anesthesiology 1989;71:260–77.
3. Fragen RJ, Hanssen EHJH, Denissen PAF, Booij LHDJ, Crul JF.

Disoprofol (ICI 35868) for total intravenous anaesthesia. Acta Anaesthesiol Scand 1983;27:113–6.

4. Persson MP, Nilsson A, Hartvig P. Relation of sedation and amnesia to plasma concentrations of midazolam in surgical patients. Clin Pharmacol Ther 1988;43:324–31.
5. Ausems ME, Hug CC, de Lange S. Variable rate infusion of alfentanil as a supplement to nitrous oxide anesthesia for general surgery. Anesth Analg 1983;62:982–6.
6. Dixon RA, Thornton JA. Tests of recovery from anaesthesia and sedation: intravenous diazepam in dentistry. Br J Anaesth 1973;45:207–13.
7. Vickers MD. The measurement of recovery from anaesthesia. Br J Anaesth 1965;37:296–302.
8. Coates DP, Monk CR, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. Anesth Analg 1987;66:64–70.
9. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The hemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia 1985;40:735–40.
10. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. Br J Anaesth 1983;55:105–11.
11. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3–9.
12. Lebowitz PW, Cote ME, Daniels AL, et al. Comparative cardiovascular effects of midazolam and thiopental in healthy patients. Anesth Analg 1982;61:771–5.
13. Boralessa H, Senior DF, Whitwam JG. Cardiovascular response to intubation. A comparative study of thiopentone and midazolam. Anaesthesia 1983;38:623–7.

Transesophageal Doppler Ultrasonography: Evidence for Improved Cardiac Output Monitoring

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PERRINO AC Jr, FLEMING J, LAMANTIA KR. Transesophageal Doppler ultrasonography: evidence for improved cardiac output monitoring. Anesth Analg 1990; 71:651–7.

Cardiac output monitoring by transesophageal Doppler ultrasound has not gained wide clinical acceptance. A recently developed transesophageal Doppler device, Accucom 2, features technological advances aimed to reduce the error of this approach to the monitoring of cardiac output. To determine if Accucom 2 enables more accurate cardiac output monitoring, a prospective investigation was undertaken. Analyses of 923 simultaneous measurements of transesophageal Doppler and thermodilution cardiac output in 47 anesthetized patients were compared. Results using Accucom 2 were highly correlated with the results obtained with thermodilution (R = 0.91) and provided significantly greater accuracy in comparison with a previously developed Doppler cardiac output monitor, Accucom 1. Technological advances in transesophageal Doppler ultrasound hold promise for clinically useful noninvasive monitoring of cardiac output.

Key Words: MONITORING, ULTRASONOGRAPHY—transesophageal Doppler. MEASUREMENT TECHNIQUES, CARDIOVASCULAR—transesophageal Doppler ultrasonography. HEART, CARDIAC OUTPUT—transesophageal Doppler ultrasonography.

Transesophageal Doppler ultrasonography offers a noninvasive alternative to thermodilution techniques for the measurement of cardiac output (CO). The basis of CO determinations by Doppler ultrasound is the product of mean aortic blood velocity and aortic cross-sectional area. Ultrasonic blood velocity measurement is calculated by the Doppler equation which relates the velocity of blood to the frequency shift of reflected ultrasound waves. Doppler signals can be reliably obtained with an ultrasound probe placed externally at the suprasternal notch and directed at the ascending aorta. Several investigations have demonstrated that this transcutaneous technique correlates well with thermodilution CO measurements (1–7).

From a monitoring perspective, the transesophageal approach has received considerable attention. The close proximity of the descending aorta to the esophagus provides an excellent window for obtaining Doppler signals. Once positioned, the transesophageal probe is stabilized by the esophagus, permitting continuous monitoring. A stationary probe is particularly advantageous for intraoperative monitoring because the repeated probe positioning required by transcutaneous techniques is time-consuming and provides only intermittent data.

The initial transesophageal Doppler CO monitors developed for clinical use, such as Accucom 1 (Datascope Corporation) and Ultracom (Lawrence Medical Systems, Inc.) share several limitations. Difficulties with these devices include improper sampling of aortic blood velocities and instability of the esophageal probe signal. Thus, transesophageal Doppler assessment of CO has yet to enjoy widespread clinical use. A recently developed transesophageal Doppler device, Accucom 2 (Datascope Corporation), features technological advances aimed at reducing these sources of error. Incorporated into Accucom 2 is a real-time display of the blood velocity profile and a digital measure of received Doppler signal strength. Mounted at the tip of a 20F esophageal probe is a continuous-wave piezoelectric transducer, transmitting a 4-MHz, 70° wide, ultrasonic beam. These features were developed to enable proper placement of the ultrasound transducers and sensitive detection of changes in probe positioning and signal quality.

The present investigation was designed to evaluate the Accucom 2 prospectively to determine if it

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Received from the Yale University School of Medicine, Department of Anesthesiology, New Haven, Connecticut. Accepted for publication August 9, 1990.

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could provide more accurate monitoring of CO. This report describes our experience with the Accucom 2 device in anesthetized patients and compares its performance to thermodilution as well as to an earlier generation transesophageal Doppler CO monitor, Accucom 1.

Methods

Ultrasonography Techniques

Doppler ultrasonographic examination was performed in 47 patients scheduled for noncardiac surgery at Yale-New Haven Medical Center following a Human Investigation Committee approved protocol. Patients with an intracardiac shunt, aortic or tricuspid valve disease, or dissecting aortic aneurysm were excluded. In those patients undergoing aortic reconstructive surgery, CO measurements were made before aortic cross-clamping. Twenty-three patients were studied with an Accucom 2 transesophageal Doppler CO monitor and 24 patients with an Accucom 1 transesophageal Doppler CO monitor.

Each device requires a three-step procedure for CO determination. First, aortic cross-sectional area is calculated by nomogram based on patient characteristics, including age, sex, height, and weight. Second, after induction of general anesthesia and tracheal intubation, the 20F esophageal probe is inserted and positioned to optimize Doppler signal. The esophageal probe also connects to an earpiece for use as a stethoscope. Third, the esophageal Doppler signals are calibrated with a transcutaneous Doppler probe placed in the suprasternal notch, which measures ascending aortic flow. Calibration of the esophageal probe is required to account for blood flow distribution to the aortic arch vessels and for the wide angle of incidence between the esophageal Doppler beam and descending aortic blood flow. The basis of the calibration procedure is calculation of a proportionality constant (K factor), which equals the ratio of ascending aortic to descending aortic blood velocity. The proportionality constant was determined in each patient at the initial calibration and was not adjusted during the procedure. Once calibrated, the transesophageal Doppler signals permit continuous measurement of stroke volume and CO based on descending aortic flow signals. These values represent the average over a 15-s interval. The monitor updates its digital display of CO every 15 s.

As a reference standard, thermodilution CO measurements were obtained at end-expiration using room-temperature injectate and a single, dedicated computer (COM-1, American Edwards). During a period of hemodynamic stability, repeated simultaneous thermodilution CO and transesophageal Doppler CO measurements were obtained and defined an epoch. For an epoch to be acceptable for analysis three to four CO values with less than 10% variation were required for each technique.

The Accucom 1 data were collected from November 1987 through August 1988. The Accucom 2 data were collected from November 1988 through June 1989. All Doppler examinations were performed by an ultrasonography team consisting of two authors (A.P., J.F.) who had previous clinical experience with Doppler ultrasonography.

Statistical Analysis

For both Accucom 1 and Accucom 2, comparison of simultaneous transesophageal Doppler CO and thermodilution CO measurements included calculation of the mean Doppler CO and mean thermodilution CO for each epoch. The means of these epochs were then analyzed by simple linear regression with calculation of the slope, intercept, and standard error of the estimate. Pearson's product-moment correlation coefficient was also determined.

The technique of Bland and Altman was used to define better the association between simultaneous Doppler and thermodilution measurements (8). The mean of the differences between simultaneous transesophageal Doppler and thermodilution measurements provides a measure of bias. The standard deviation of the difference between simultaneous measurements is a measure of the accuracy of Doppler measurements in estimating thermodilution measurements. The mean absolute percent error represents the error in the Doppler technique as a percentage of actual CO. With the Bland and Altman method, the actual CO for an epoch is defined as the mean of the Doppler and thermodilution measurements. This definition limits the statistical bias caused by measurement errors inherent in the thermodilution technique. Cardiac output measurement, as with many biological measurements, has no absolute gold standard. Thermodilution represents an imperfect, but widely accepted, standard for clinical CO measurement (9). The actual CO during any epoch is thus unknown, and, for statistical purposes, the mean of the transesophageal Doppler and thermodilution measurements is considered the best approximation (8). Both Accucom 1 and Accucom 2 data were compared with thermodilution data by the Bland and Altman method.

Student's *t*-test and *F*-test were used to determine

Table 1. Patient Demographics

	Age (yr)	Height (cm)	Weight (kg)
Accucom 1	65.8 ± 11.2	173 ± 10	72.8 ± 16.3
Accucom 2	66.2 ± 10.5	170 ± 14	70.7 ± 14.6

All values are expressed as mean ± SD.

Both groups consist primarily of elderly patients. There are no significant differences in age, height, or weight.

if statistically significant improvements in the association between Doppler and thermodilution measurements occur with the use of Accucom 2 as compared with Accucom 1. In both tests a *P* value of less than 0.05 was considered to be statistically significant.

Data were also analyzed to determine if operator experience influenced the performance of these CO monitors. For each device, data from the first half of the patient population were compared with data from the second half. A Student's *t*-test was performed, with $P < 0.05$ considered to be statistically significant.

Results

Three patients in the Accucom 1 group and one patient in the Accucom 2 group were excluded because of poor Doppler signal quality. Demographics of the patient population are summarized in Table 1. There were no significant differences in age, height, or weight between the study groups.

A total of 923 paired Doppler and thermodilution determinations were made in 43 patients. Cardiac output determinations were divided into 291 epochs for data analysis; each epoch consisted of three to four paired CO determinations during a hemodynamically stable period of less than 5 min. The distribution of measurements of CO was similar in both groups with a range of 2.0–10.0 L/min (Figure 1).

The scattergrams and regression analysis of the data are shown in Figure 2. The Accucom 2 data show an excellent correlation with thermodilution ($R = 0.91$), one higher than that found in the Accucom 1 group ($R = 0.72$).

To demonstrate better the agreement between Doppler and thermodilution measurements, the technique of Bland and Altman was chosen (8). Figure 3 is a plot of the difference between simultaneous thermodilution and Doppler measurements. The mean difference (bias) and two standard deviation range are also plotted. Accucom 2 shows close agreement with thermodilution throughout the CO range and was more accurate than Accucom 1. This was dem-

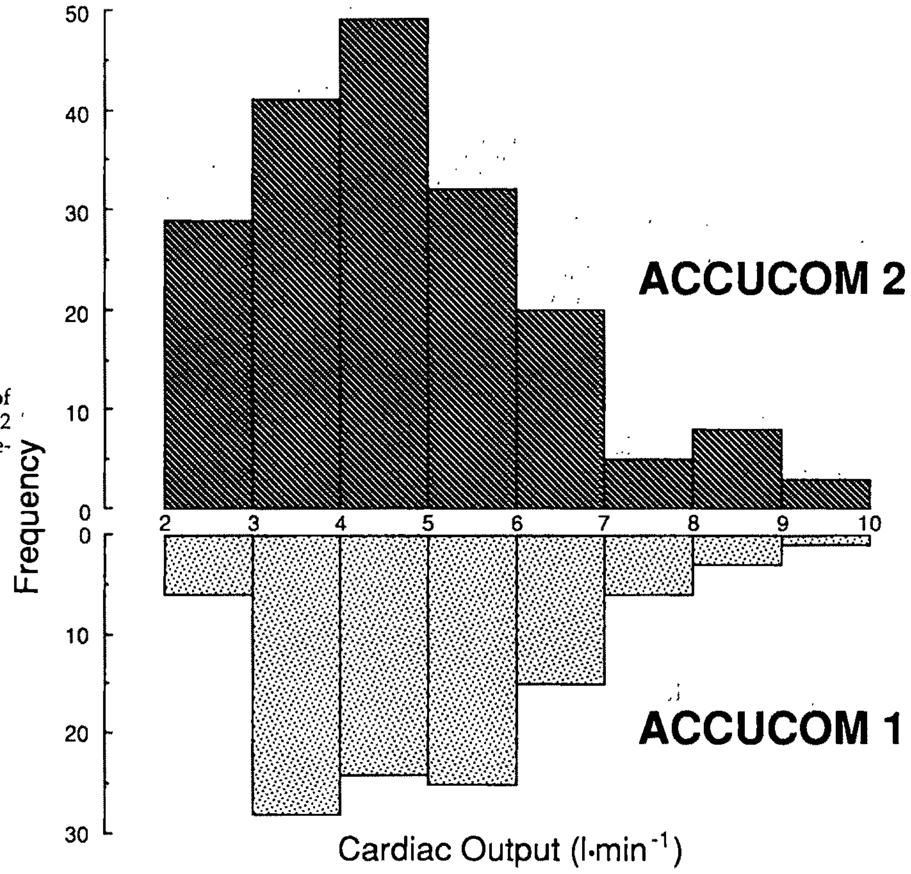

Figure 1. Distribution of measurements of CO for the Accucom 1 and Accucom 2 groups. Ranges and means of CO measurements are similar for both groups.

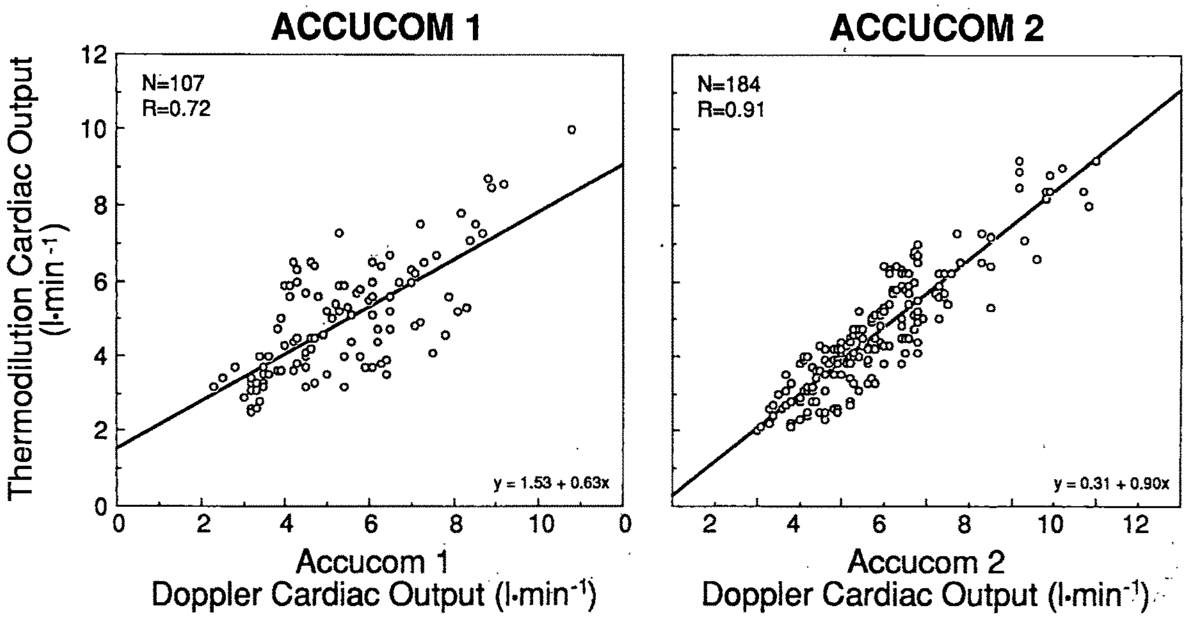

Figure 2. Scattergram of simultaneous transesophageal Doppler and thermodilution CO measurements. Accucom 2 data shows improved correlation with thermodilution measurements.

onstrated by statistically significant reductions in bias, standard deviation, and mean absolute percent error ($P < 0.05$).

The effects of operator experience were examined by comparing the performance of each Doppler device on the first half of the study group with the second half. There was no improvement in accuracy as measured by bias, standard deviation, and mean absolute percent error for either Accucom 1 or Accucom 2 with increased operator experience (Figure 4).

Discussion

Transesophageal Doppler ultrasound is a noninvasive technique for the continuous monitoring of CO. The inherent safety of transesophageal Doppler extends the applicability of CO monitoring to a broader spectrum of patients. However, transesophageal Doppler CO monitoring has performed inconsistently in anesthetized patients (10–13). A study of 16 patients undergoing aortocoronary bypass surgery found a poor correlation between transesophageal Doppler and thermodilution measurements ($R = 0.43$) (10). Analysis of this study revealed that calibration of the esophageal probe was a major source of error in the Doppler measurements. An average correlation coefficient of 0.67 (range, −0.02–0.99) was reported with transesophageal Doppler monitoring in 23 surgical patients (11). The investigators concluded that the operator-dependent nature of the Doppler technique contributed to the inconsistent results. In a separate study, Accucom 1 was used in 25 patients after aortocoronary bypass surgery (12). The investigators concluded that the standard error of the estimate of 1.4 L/min was unacceptably large for clinical monitoring. Consequently, technical refinements in transesophageal Doppler CO measurements were undertaken to improve the accuracy of the technique.

Emphasis has been focused on reducing those errors associated with improper sampling of aortic flow velocities and instability of the esophageal probe signal. Our data support the hypothesis that technological advances in Doppler ultrasound, as engineered in Accucom 2, improve the accuracy of CO monitoring. Accucom 2 data demonstrated excellent correlation with thermodilution measurements and provided greater accuracy over Accucom 1, as demonstrated by significant reductions in bias, standard deviation, and mean absolute percent error.

Accucom 2 incorporates both real-time blood velocity profile and digital signal strength display to aid in the proper positioning of the ultrasound transducers. We believe that these features are at least partially responsible for the improved performance. Calibration of the esophageal probe is accomplished with a transcutaneous probe placed at the suprasternal notch. For accurate CO measurements the suprasternal probe must be aimed nearly parallel to the high-velocity core of ascending aortic flow. With the

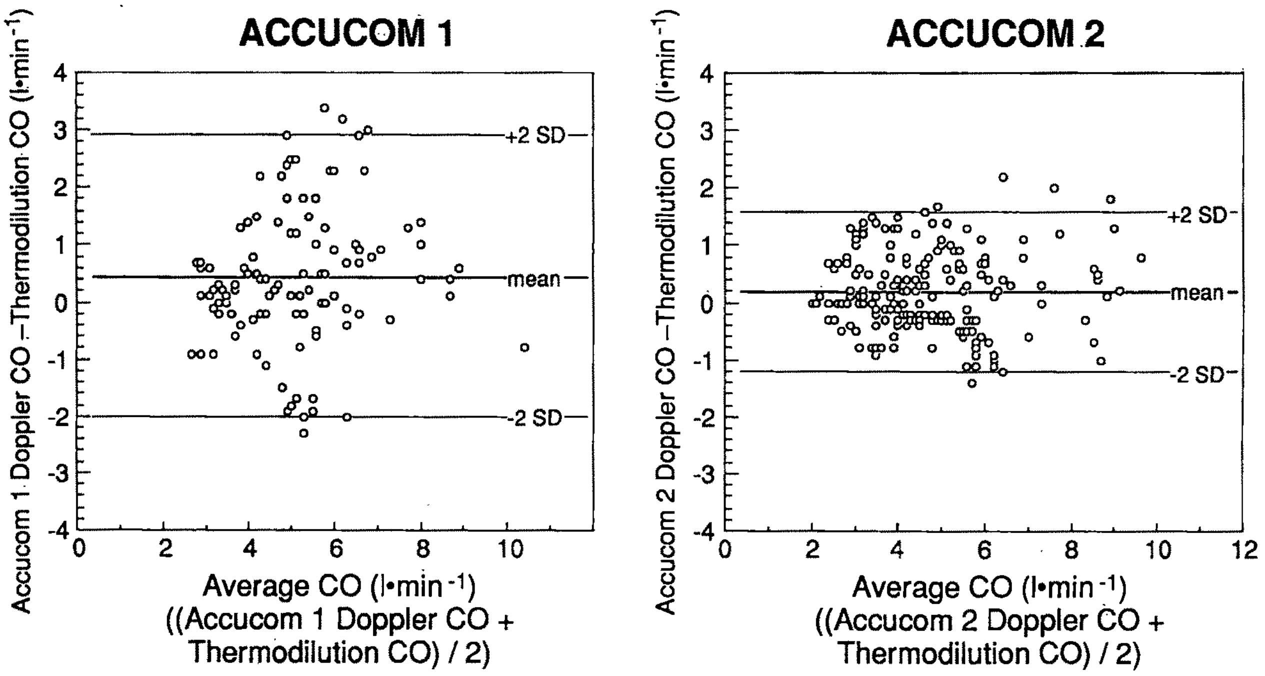

Figure 3. To illustrate better the agreement between transesophageal Doppler and thermodilution CO measurements, the data are presented by the technique of Bland and Altman. The difference between simultaneous Doppler and thermodilution CO measurements is plotted against the average CO. Agreement between transesophageal Doppler and thermodilution measurements is significantly greater with Accucom 2.

Accucom 2 device, proper positioning of the suprasternal probe was recognized as having maximal signal strength and a sharply defined velocity profile. This was a more objective procedure than relying solely on the audible Doppler frequency shift as required with Accucom 1. The displays also aided the detection of nonaortic flow signals (e.g., innominate artery flow) that result in erroneous CO measurements. Additionally, during use of Accucom 2 the displays enabled early recognition of a decay in the esophageal Doppler signal, thereby alerting the physician to the need for repositioning the probe.

The 4-MHz, 70° wide-beam esophageal transducer designed for the Accucom 2 provided excellent Doppler signals. Earlier designs utilized a 3-MHz, 40°-wide-beam transducer. The modifications in beam width and ultrasonic frequency result in a larger ultrasound field. The wide field is an advantage under conditions such as positive pressure ventilation, where movement of mediastinal structures including esophagus and aorta during the ventilatory cycle can cause instability in the esophageal Doppler signal. The variability in Accucom 2 transesophageal Doppler measurements within an epoch was extremely low except during electrical cautery, which caused easily recognizable electrical interference.

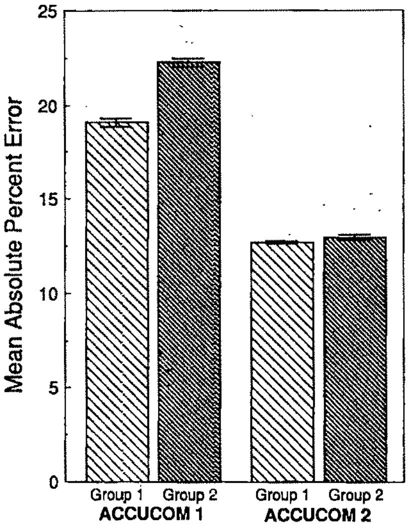

Figure 4. Effect of operator experience on Doppler performance. For both devices, increased operator experience (group 2) did not result in improved accuracy.

Doppler CO measurements require the determination of aortic cross-sectional area and blood velocity. Both Accucom 1 and Accucom 2 determine ascending aortic cross-sectional area by nomogram based on age, sex, height, and weight of the patient. This approach has the advantage of not requiring an independent ultrasound measurement of aortic diameter. Intraoperative A-mode ultrasonic determinations of aortic cross-sectional area can be time-consuming and may not correlate well with open-chest measurements of aortic cross-sectional area (11). The use of two-dimensional echocardiography rather than A-mode or M-mode to assess aortic dimensions would appear to be advantageous (14). Although the accuracy of the nomogram method has yet to be defined, the benefits gained in time and ease of measurement are welcomed. The three-step procedure for obtaining transesophageal Doppler CO measurements with the Accucom 2 requires 5–15 min. Validation of the nomogram for calculating aortic cross-sectional area is needed. Fortunately, errors in cross-sectional area measurements result in a calibration error only and do not interfere with trending capabilities (10).

Other sources of error in the transesophageal Doppler technique should be addressed. In particular, the proportionality constant (K factor) that relates descending aortic and ascending aortic blood velocities can change in the course of the operation. Accucom 2 calculates the proportionality constant for each patient during the initial calibration, and in our study this was not adjusted during the operation. Significant fluctuations in the proportionality constant during surgery would result in error. Several studies have addressed this issue. For example, expansion of the descending aorta in response to increasing aortic blood pressure would affect the calibration constant. Studies in sheep and in humans have demonstrated alterations of aortic diameter with blood pressure changes (15,16). Also, surgical stress and changes in anesthetic depth could potentially shift the proportion of blood flow to the head and upper extremities. Alterations in the K factor with the addition of enflurane to the anesthetic have been demonstrated (17). There is also evidence that manipulation of the aorta, as seen during open-heart surgery and aortic reconstructive operations, may induce additional inaccuracies (10,18). Further evaluation of the effect of these factors on Doppler performance is required.

Method comparison studies are best performed using a randomized and double-blinded technique. In this study, an investigator blinded to the type of Doppler monitor was not workable due to the interactive nature of Doppler monitoring. Doppler and thermodilution comparisons result from data collected simultaneously, but we also compared Accucom 2 data with previously collected Accucom 1 data. Although this approach has the advantage of the operators familiarizing themselves with each machine through repetitive use, the improved monitoring may result from either operator or design improvements. In this investigation a single ultrasound team with previous clinical experience in Doppler ultrasonography performed all Doppler examinations. We found no data to support the hypothesis that improved operator skills are responsible for the marked improvements in monitoring performance. Increased operator experience did not lower the bias, standard deviation, or mean absolute percent error between transesophageal Doppler and thermodilution CO measurements. This was true for both Accucom 1 and Accucom 2. Although training in transesophageal ultrasonography is a prerequisite for proper use of these monitors, this study demonstrates that even experienced operators were unable to obtain a satisfactory degree of accuracy with Accucom 1. The engineering refinements incorporated into Accucom 2 were essential to the marked improvement in accuracy.

In conclusion, technological advances in transesophageal Doppler, including real-time velocity profile, digital signal-strength display, and improved esophageal probe design, result in more accurate CO measurements. Such devices hold promise for clinically useful noninvasive monitoring of CO.

References

1. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man—clinical validation. Circulation 1983;67:593–602.
2. Nishimura RA, Callahan MJ, Scharf HV, Ilstrup DM, Miller FA, Tajik AJ. Noninvasive measurement of cardiac output by continuous-wave Doppler echocardiography: initial experience and review of the literature. Mayo Clin Proc 1984;59:484–9.
3. Chandraratna PA, Nanna M, McKay C, et al. Determination of cardiac output by transcutaneous continuous-wave ultrasonic Doppler computer. Am J Cardiol 1984;53:234–7.
4. Rose JS, Nanna M, Rahimtoola SH, Elkayam U, McKay C, Chandraratna AN. Accuracy of determination of changes in cardiac output by transcutaneous-wave Doppler computer. Am J Cardiol 1984;54:1099–101.
5. Ihlen H, Amlie JP, Dale J, et al. Determination of cardiac output by Doppler echocardiography. Br Heart J 1984;51:54–60.
6. Ihlen H. Myhre E, Amlie JP, Forfang K, Larsen S. Changes in left ventricular stroke volume measured by Doppler echocardiography. Br Heart J 1985;54:378–83.
7. Bojanowski LM, Timmis AD, Youssef CN, Gosling RG. Pulsed Doppler ultrasound compared with thermodilution for monitoring cardiac output responses to changing left ventricular function. Cardiovasc Res 1987;21:260–8.
8. Bland JH, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;i:307–10.
9. Levitt JM, Replogle RL. Thermodilution cardiac output: a critical analysis and review of the literature. J Surg Res 1979; 27:392–404.
10. Mark JE, Steinbrook RA, Gugino LD, et al. Continuous noninvasive monitoring of cardiac output with esophageal Doppler ultrasound during cardiac surgery. Anesth Analg 1986;65: 1013–20.

11. Freund PR. Transesophageal Doppler scanning versus thermodilution during general anesthesia. Am J Surg 1987;153:490–503.
12. Spahn DR, Schmid ER, Tornic M, et al. Continuous noninvasive cardiac output monitoring by electrical bioimpedance and transesophageal continuous wave Doppler ultrasound. Anesthesiology 1988;69:A236.
13. Siegal LC, Shafer SL, Martinez GM, et al. Comparison of simultaneous intraoperative measurements of cardiac output by thermodilution, esophageal, Doppler and electrical impedance in anesthetized patients. Anesthesiology 1987;67:A181.
14. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;54:507–12.
15. List W, Gravenstein N, Banna T, et al. Interaction in sheep between mean arterial pressure and cross-sectional area of the descending aorta: implications for esophageal Doppler monitoring. Anesthesiology 1987;67:A178.
16. Hillel Z, Zane E, Thys D. Systemic arterial blood pressure influences the cross-sectional area of the descending thoracic aorta. Anesthesiology 1988;69:A11.
17. Thys DM, Hillel Z. Can the K-factor be a source of inaccuracy in the determination of esophageal Doppler cardiac output? Anesthesiology 1988;69:A2392.
18. Perrino AC, Fleming J, LaMantia KR. Transesophageal Doppler cardiac output monitoring: evidence for improved accuracy during aortic reconstructive surgery (abstract). Anesth Analg 1990;70:S306.

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1990;71:658–64

Elimination Kinetics of Sevoflurane and Halothane From Blood, Brain, and Adipose Tissue in the Rat

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STERN RC, TOWLER SC, WHITE PF, EVERS AS. Elimination kinetics of sevoflurane and halothane from blood, brain, and adipose tissue in the rat. Anesth Analg 1990;71:658–64.

Using the rat as an animal model, the elimination kinetics of sevoflurane and halothane from brain, blood, and adipose tissue were compared. Elimination of sevoflurane and halothane from blood and brain was biexponential. The rapid, α-elimination rates of sevoflurane from blood and brain were faster than the corresponding rates for halothane. However, the slower β-elimination rates from brain and blood, as well as the elimination rates from adipose tissue, were similar for both volatile anesthetics. Thus, the potential for residual postoperative impairment from subanesthetic tissue concentrations of halothane and sevoflurane may be similar even though sevoflurane is initially eliminated more rapidly from blood and brain.

Key Words: ANESTHETICS, VOLATILE—halothane, sevoflurane. PHARMACOKINETICS, HALOTHANE, SEVOFLURANE.

Sevoflurane provides for a more rapid emergence from general anesthesia than that provided by currently used volatile agents in several animal species, including humans (1–4). This favorable recovery profile is believed to be a consequence of the low solubility of sevoflurane in blood. However, it is also important to consider the rate of elimination of anesthetics from body stores. This is because residual subanesthetic concentrations of these drugs may be associated with postoperative impairment of psychomotor and physiologic function (5,6).

Yasuda et al. (7) have recently reported partition coefficients for sevoflurane in a variety of human tissues. They report that the blood/gas partition coefficient ($\lambda_{B/G}$) of sevoflurane is lower than those of halothane and isoflurane, but that the tissue/blood partition coefficients ($\lambda_{T/B}$) of sevoflurane for fat, muscle, brain, and other human tissues are similar to those of halothane and isoflurane. From these data, it might be predicted that sevoflurane would initially be eliminated more rapidly from blood than isoflurane or halothane, but that long-term elimination of all three drugs from body stores would proceed at similar rates. This is because the initial rate of elimination (α-elimination) of anesthetics from tissue is considered to be a function of its $\lambda_{B/G}$, whereas the long-term elimination rate (β-elimination) of anesthetics from body stores is considered to be a function of its $\lambda_{T/B}$ (8).

These predictions were tested in an animal model by comparing the elimination rates of halothane and sevoflurane from several different tissues. This was done by anesthetizing rats for 1 h with equieffective concentrations of halothane or sevoflurane and then directly measuring the anesthetic concentrations in blood, brain, and adipose tissue at various times after discontinuation of the anesthetic.

Materials and Methods

Materials

Male Sprague–Dawley rats weighing 250–300 g were obtained from Sasco, Inc. (Omaha, Neb.) and were cared for in the Washington University Animal Care Facility. All animal studies performed received approval from the Washington University Committee on Humane Care of Laboratory Animals. Chemicals

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Supported by the Ambulatory Anesthesia Research Foundation (Los Altos, Calif.), NIH grant R01-37846 (A.S.E.), and a Burroughs-Wellcome/Foundation for Anesthesia Education and Research fellowship grant (R.C.S.).

Received from the Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri. Accepted for publication August 7, 1990.

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used were obtained from the following commercial sources: diethyl ether and *n*-heptane from Fischer Scientific (Fair Lawn, N.J.); halothane from Ayerst Laboratories (New York, N.Y.); sevoflurane from Maruishi Pharmaceuticals (Osaka, Japan).

Measurement of Elimination Kinetics

Rats were anesthetized in a 5-L chamber into which 4 L/min of anesthetic-containing gas in 100% oxygen was delivered. Anesthetics were delivered using calibrated temperature-compensated vaporizers and anesthetic concentrations in gas verified by a previously described gas chromatographic method (9). After a 1-h exposure to either 3 vol% sevoflurane or 1.5 vol% halothane (1.3 × MAC concentrations), groups of three rats were removed from the anesthetic chamber and killed at set times after discontinuing the anesthetic exposure. To ensure adequate anesthesia when the rats were killed at times beyond 1 min, these animals were additionally anesthetized with diethyl ether just before being killed. Blood samples were obtained at the desired times by surgically exposing the abdominal aorta and anaerobically withdrawing blood through a 21-gauge needle into a gas-tight syringe. The animals were then decapitated, their brains dissected free, and the hemicortices isolated for anesthetic extraction. Subsequently, the abdomen was reexplored and the retroperitoneal fat dissected free for measurement of anesthetic concentrations.

^{19}F-Nuclear Magnetic Resonance Method for Measuring Anesthetic Concentrations in Adipose Tissue

A nuclear magnetic resonance (NMR) spectroscopic method was developed for measuring sevoflurane and halothane concentrations in adipose tissue because of the anticipated difficulty of quantitating low anesthetic concentrations in adipose tissue using gas chromatographic methods. This method does not require extraction of drug from tissue.

Samples of retroperitoneal adipose tissue were surgically removed and immediately placed in 5-mL syringes. Air was expelled from the syringes and the adipose tissue injected through PE-240 tubing into 5-mm NMR tubes that were then sealed and stored at 4°C until analysis, which was within 24 h. To analyze the samples, they were allowed to warm to room temperature (22.7°C) and a capillary tube containing methoxyflurane (10 mM) in $CDCl_3$ was inserted into the NMR tube. The difluoromethylene group of methoxyflurane served as a concentration and chemical shift reference. The same capillary was used to obtain spectra on all standards and samples. The CF_2 group of methoxyflurane was arbitrarily assigned at 0.00 ppm; the CF_3 groups of sevoflurane and halothane (in adipose tissue) resonated at 12.1 and 10.4 ppm, respectively. These signals were distinct and specific for each anesthetic. Note that parts per million (ppm) refers to the NMR chemical shift scale and is not a unit of concentration.

To calibrate the NMR measurements, standard samples of halothane and sevoflurane were prepared in chloroform to give concentrations of 1, 3, 10, and 20 mM. These liquid samples were placed in 5-mm NMR tubes. A methoxyflurane external reference capillary was then inserted into the tubes, and ^{19}F-NMR spectra were collected (room temperature) at 470.3 MHz on a Varian VXR-500 multinuclear spectrometer. Acquisition parameters for all ^{19}F spectra were as follows: pulse width 7 μs, acquisition time 0.5 s, and interpulse delay 10 s. Four transients were collected for all samples and standards, and exponential line broadening of 2 Hz was applied to all spectra. The features corresponding to the trifluoromethyl groups of sevoflurane and halothane and to the difluoromethylene group of methoxyflurane were electronically integrated. The ratio of the CF_3 peak area to the CF_2 peak area was plotted as a function of anesthetic standard concentration to generate a standard curve. For both sevoflurane and halothane, correlation coefficients for these standard curves were 0.999. These standard curves were then used to calculate anesthetic adipose tissue concentrations from the CF_3/CF_2 ratios obtained with adipose tissue samples.

The accuracy of anesthetic measurements made by NMR was assessed by concurrent NMR and gas chromatographic measurement of anesthetic concentrations in the same piece of adipose tissue. We found that the anesthetic concentrations in adipose tissue measured by gas chromatography were consistently 20% (halothane) and 8% (sevoflurane) higher than anesthetic concentrations measured by NMR. This may be due to differences in the magnetic field susceptibility of anesthetics in chloroform and adipose tissue. Although the anesthetic concentrations in adipose tissue measured by NMR may be less than actual values, the offset in concentrations does not affect the absolute value of the time constants of elimination of anesthetic from adipose tissue.

Using these methods and accepting a minimum signal-to-noise ratio of 10, concentrations of halothane and sevoflurane as low as 0.2 and 0.1 mM could be measured in adipose tissue. Examples of the

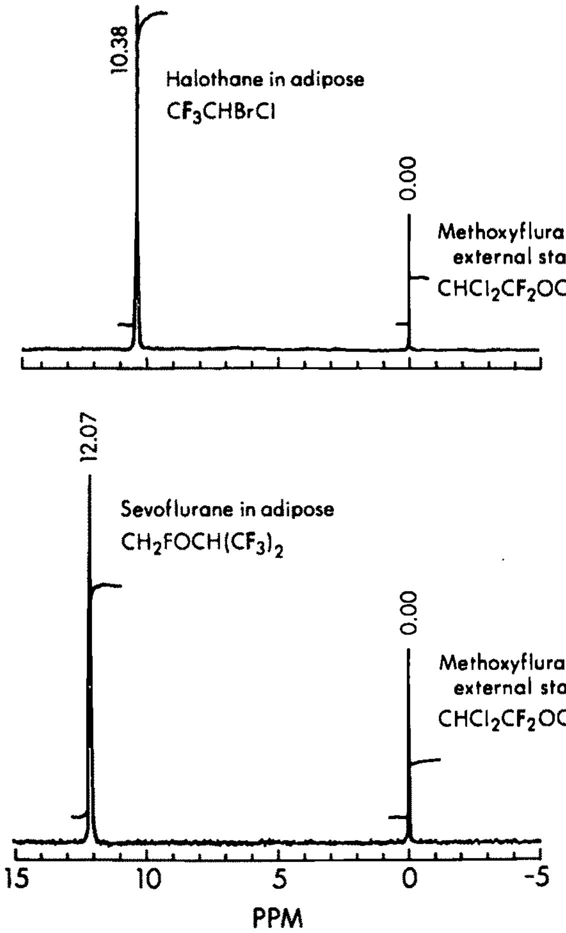

Figure 1. ^{19}F-NMR spectra at 470.3 MHz of halothane and sevoflurane in adipose tissue. The feature at 0 ppm represents the CF_2 group of methoxyflurane in an external reference capillary. This served as a concentration and chemical shift reference. The feature at 10.38 ppm is the CF_3 group of halothane in adipose tissue from a rat after 2 h of recovery from halothane anesthesia. The feature at 12.07 ppm is the CF_3 group of sevoflurane in adipose tissue from a rat after 2 h of recovery from sevoflurane anesthesia. Both spectra were collected at room temperature under quantitative conditions and represent the accumulation of four transients.

spectra of halothane and sevoflurane in adipose tissue are shown in Figure 1.

Gas Chromatographic Measurement of Anesthetic Concentrations in Brain and Adipose Tissue

Anesthetic concentrations in brain and adipose tissue were measured using a modified version of a previously reported method that entailed organic extraction of isoflurane from blood and subsequent gas chromatographic analysis (9). The following modifications were made:

1. To facilitate the extraction of anesthetic from brain and adipose tissue, the tissues were homogenized in *n*-heptane with a Tekmar SDT Tissumizer for 10 s and the aqueous and organic phases subsequently separated by centrifugation.

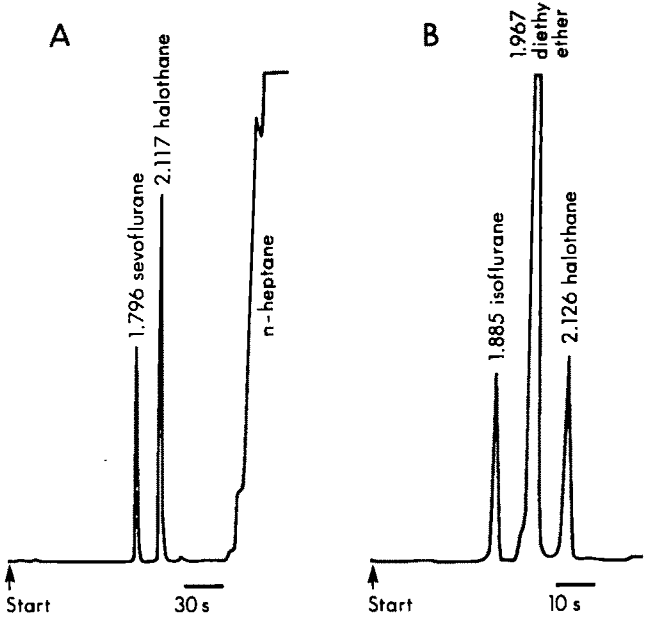

Figure 2. Gas chromatographic separation of isoflurane, sevoflurane, diethyl ether, and halothane. *Panel A* shows a chromatogram of sevoflurane extracted from the blood of a rat anesthetized with sevoflurane for 1 h. Halothane is used as the internal standard. Note that the solvent (*n*-heptane) runs later than the anesthetics because of its lower volatility. *Panel B* shows a chromatogram of halothane extracted from the brain of a rat 10 min after the termination of the halothane anesthetic. Note that diethyl ether is present in this sample due to the necessity for reanesthetization of the animal before killing it. Isoflurane serves as an internal concentration standard. Also note the faster chart-recording speed in this trace compared with panel A.

2. For measurement of sevoflurane and halothane concentrations in adipose and brain tissue an internal standard of either halothane or isoflurane was used (isoflurane was used as the internal standard for the measurement of halothane in tissue, and halothane for the measurement of sevoflurane in tissue). Gas chromatographic retention times of sevoflurane, isoflurane, and halothane were 1.78, 1.86, and 2.1 min, respectively. The flame ionization detector response ratios for isoflurane to halothane (0.59) and for sevoflurane to halothane (0.95) were constant over the concentration ranges studied. The presence of diethyl ether (retention time, 1.94 min) did not interfere with the measurement of these signals. Examples of the gas chromatographic separation of the different anesthetics are shown in Figure 2.
3. Extraction of sevoflurane and halothane from brain and adipose tissue was performed using *n*-heptane/tissue ratios (vol/vol) of 6:1 for brain

and 30:1 for adipose tissue. In this way >90% of sevoflurane and halothane could be extracted from brain and adipose tissue. Because of the large volume of *n*-heptane required to efficiently extract anesthetic from adipose tissue, only relatively high concentrations (0.5–1.0 mM) of anesthetic in adipose tissue could be reliably quantitated using gas chromatography.

Measurement of Partition Coefficients

Brain, blood, and adipose tissue/gas partition coefficients were measured for both sevoflurane and halothane. Initially, homogenate/gas partition coefficients were measured for each tissue. Tissue homogenates were prepared by taking one part tissue, adding it to three parts 0.9% NaCl (vol:vol), and homogenizing for 10 s in a Tekmar tissumizer. Samples of the tissue homogenates (0.2–0.5 mL) were added to 250-mL gas sampling bulbs containing 2–4 vol% of anesthetic. The bulbs were incubated with continuous shaking for 60 min at 37°C. Preliminary experiments showed that this was a sufficient length of time for complete equilibration to occur between the gas phase and the homogenate. At the end of the equilibration period, anesthetic concentrations in the gas phase and in the homogenate were measured by gas chromatography as described above. The saline/gas partition coefficients ($\lambda_{saline/gas}$) of sevoflurane and halothane were measured using the same method.

Calculations of adipose and brain tissue concentrations were based on the assumption that the concentration in the homogenate was equal to the weighted average of the concentrations of anesthetic in saline and tissue (Equations [1] and [2]). Given that the relative volumes of saline and tissue in the homogenate and the $\lambda_{saline/gas}$ were known, the anesthetic concentration in tissue could be calculated. Ultimately, the tissue/gas partition coefficient ($\lambda_{T/G}$) was determined by dividing the tissue concentration by the anesthetic concentration in gas. The adipose tissue/gas partition coefficients ($\lambda_{adipose/gas}$) measured using these techniques were in agreement with those determined by Yasuda et al. (7):

$$C_{homogenate} = 0.25C_{tissue} + 0.75C_{saline}, \qquad (1)$$

where C = anesthetic concentration.

$$C_{tissue} = 4(C_{homogenate} - 0.75C_{gas} \cdot \lambda_{saline/gas}), \qquad (2)$$

by rearrangement and substitution (see text).

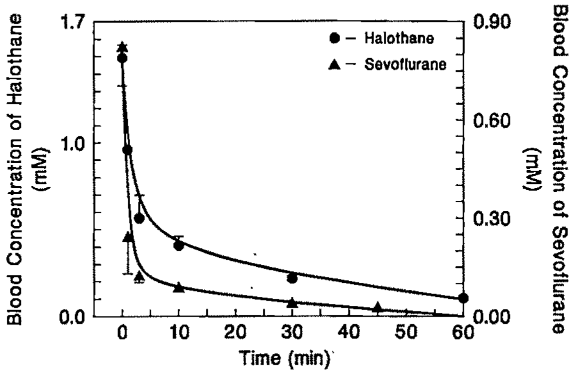

Figure 3. The elimination kinetics of halothane and sevoflurane from blood. Animals were anesthetized with either 1.5 vol% halothane or 3 vol% sevoflurane for 1 h, and blood was obtained at the indicated times after discontinuation of the anesthetic. Data points represent the average of anesthetic concentration measurements in blood from three rats ± SEM. Curves represent the exponential fits of the data generated using a nonlinear least-squares method. Note that to make relative comparisons of anesthetic elimination from blood, halothane and sevoflurane concentrations are scaled to the calculated equilibrium concentration of anesthetic in blood (indicated at the top of the *y*-axis).

Statistical Analysis

Data for kinetic time points and partition coefficients represent the mean ± SEM of three measurements. Curve fitting for pharmacokinetic analyses was performed using a nonlinear least-squares curve-fitting program, NFITS (edited by Dr. C. J. Lingle). Blood and brain elimination kinetics were best fit by a biexponential function of elimination. A uniexponential function of elimination was sufficient to fit the elimination kinetics of anesthetic from adipose tissue. Time constants (the inverse of rate constants) are used instead of rate constants to describe the kinetic data to make the comparison of elimination kinetics more comprehensible, and are reported ±90% confidence limits. τ_1 is the inverse of the rate constant of α-elimination and τ_2 is the inverse of the rate constant of β-elimination. Multiple comparisons of elimination time constants were made using a one-way analysis of variance followed by a Bonferroni multiple comparisons test. Single comparisons were made using a Student's *t*-test. Statistically significant differences were defined as $P < 0.05$.

Results

After 1 h of anesthetic administration, halothane and sevoflurane concentrations in blood and brain increased to 80%–90% of their predicted equilibrium concentrations (Figures 3 and 4). Estimates of equilibrium concentrations were calculated as the product

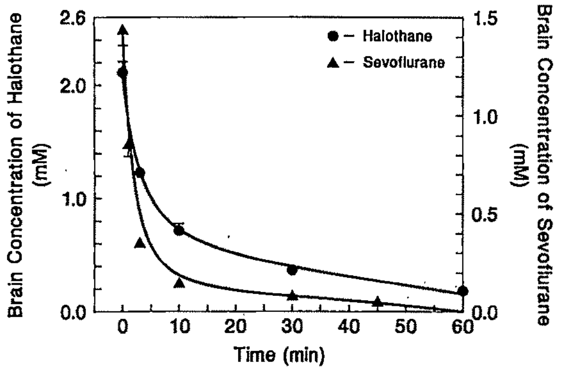

Figure 4. The elimination kinetics of halothane and sevoflurane from brain. Animals were anesthetized with either 1.5 vol% halothane or 3 vol% sevoflurane for 1 h, and tissue was obtained at the indicated times after discontinuation of the anesthetic. Data points represent the average measurement of anesthetic concentrations in the brains of three rats ±SEM. Curves represent the exponential fits of the data generated using a nonlinear least-squares method. Note that to make relative comparisons of anesthetic elimination from brain, halothane and sevoflurane concentrations are scaled to the calculated equilibrium concentration of anesthetic in brain (indicated at the top of the y-axis).

Table 1. Anesthetic Elimination Time Constants

	α-Elimination τ_1 (min)	β-Elimination τ_2 (min)
Blood		
Sevoflurane	0.58 ± 0.03	26 ± 5.0
Halothane	1.29 ± 0.15[a]	36 ± 5.6
Brain		
Sevoflurane	1.60 ± 0.10	34 ± 11
Halothane	2.70 ± 0.66[a]	34 ± 7.8
Adipose		
Sevoflurane	—	241 ± 53
Halothane	—	246 ± 51

Values are time constants of elimination of halothane and sevoflurane from blood, brain, and adipose ±90% confidence limits.

[a] $P < 0.05$ compared with sevoflurane value for same tissue.

Table 2. Anesthetic Partition Coefficients

Partition	Halothane	Sevoflurane
$\lambda_{blood/gas}$	2.79 ± 0.1	0.75 ± 0.03
$\lambda_{brain/gas}$	4.6 ± 0.1	1.27 ± 0.06
$\lambda_{adipose/gas}$	112 ± 1.4	38.8 ± 2.5
$\lambda_{saline/gas}$	0.67 ± 0.03	0.30 ± 0.04
$\lambda_{brain/blood}$	1.64	1.69
$\lambda_{adipose/blood}$	40	52

Except for $\lambda_{brain/blood}$ and $\lambda_{adipose/blood}$, all values are mean ± SEM. The $\lambda_{tissue/gas}$ and $\lambda_{saline/gas}$ for halothane and sevoflurane in rat tissues were measured using gas chromatographic techniques described in Methods. $\lambda_{tissue/blood}$ was calculated by dividing $\lambda_{tissue/gas}$ by $\lambda_{blood/gas}$.

of the $\lambda_{T/G}$ and the concentration of anesthetic in inspired gas (calculated according to the ideal gas laws). Although brain and blood have achieved near-equilibration with anesthetic in inspired gas after 1 h, concentrations in adipose tissue are less than 25% of predicted equilibrium values. This is because adipose tissue has a large capacity for anesthetic and a relatively small blood flow.

Once anesthetic administration was terminated, elimination of anesthetic from blood and brain proceeded in a biexponential fashion in both halothane- and sevoflurane-anesthetized animals (Figures 3 and 4). Anesthetic elimination from brain closely paralleled that from blood, consistent with the fact that brain has a relatively high blood flow and a low capacity for anesthetic. As expected, the elimination (α-elimination) of sevoflurane from blood ($\tau = 0.58 \pm 0.03$ min) proceeds at a rate more than two times faster than α-elimination of halothane from blood ($\tau = 1.29 \pm 0.15$ min) ($P < 0.05$). Similarly, the α-elimination of sevoflurane from brain ($\tau = 1.60 \pm 0.10$ min) proceeds faster than that of halothane ($\tau = 2.70 \pm 0.66$ min) ($P < 0.05$).

In contrast to α-elimination, β-elimination time constants for sevoflurane and halothane from blood and from brain were similar (Table 1). The time constants for β-elimination from blood and brain reflect the rate of elimination of anesthetic from total body stores, implying that the rate of elimination of the two anesthetics from body stores is similar. This is consistent with the notion that the rate of β-elimination of anesthetics from total body stores is directly related to the tissue/blood solubility of anesthetic and the observation that the tissue/blood partition coefficients of halothane and sevoflurane are similar (Table 2).

The kinetics of anesthetic elimination from adipose tissue are obviously different than those of blood and brain (Figure 5). When anesthetic administration is discontinued, anesthetic concentrations in adipose tissue decrease slowly and in a uniexponential fashion. Similar to β-elimination of anesthetics from blood and brain, the time constants for elimination of both anesthetics from adipose tissue are not significantly different: the time constants of elimination are 246 ± 51 min and 241 ± 53 min for halothane and sevoflurane, respectively. This is consistent with the observation that the $\lambda_{adipose/blood}$ of the two anesthetics are similar (Table 2).

Discussion

In the rat, sevoflurane is initially eliminated from blood and brain at a faster rate than halothane. These data are consistent with previous reports (1–4) and with the concept that $\lambda_{B/G}$ is a principal determinant of the initial rate of volatile anesthetic elimination.

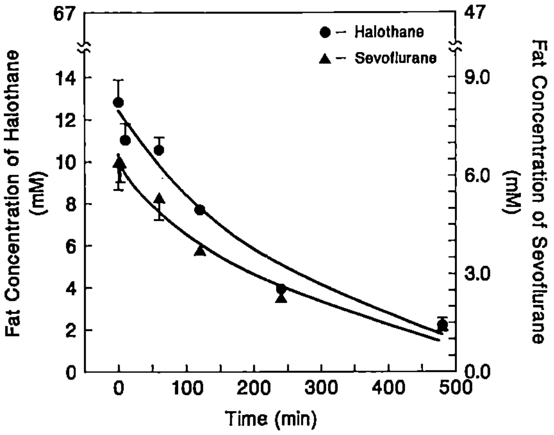

Figure 5. The elimination kinetics of halothane and sevoflurane from adipose tissue. Animals were anesthetized with either 1.5 vol% halothane or 3 vol% sevoflurane for 1 h, and tissue was obtained at the indicated times after the discontinuation of the anesthetic. Data points represent the average of three determinations ± SEM. Curves represent the exponential fits of the data generated using a nonlinear least-squares method. Note that to make relative comparisons of anesthetic elimination from adipose tissue, halothane and sevoflurane concentrations are scaled to the calculated equilibrium concentration of anesthetic in adipose tissue (indicated at the top of the y-axis).

The α-elimination rate of anesthetic elimination from adipose tissue could not be determined. This is because the blood flow to fat is low and the anesthetic capacity of adipose tissue is high. Thus, the amount of anesthetic eliminated from fat during the rapid decrease in anesthetic concentrations in blood (α-elimination) is relatively small and undetectable; only β-elimination of anesthetic from adipose tissue can be observed. Theoretically, if α-elimination from adipose tissue could be observed, τ_1 of adipose tissue would also be predicted to be smaller in sevoflurane-anesthetized animals.

In contrast to α-elimination rates, longer-term, β-elimination of halothane and sevoflurane from blood, brain, and adipose tissue proceeds at similar rates. This observation is consistent with the hypothesis that $\lambda_{T/G}$ is a principal determinant of β-elimination from body stores. To the best of our knowledge these are the only data that confirm by direct measurement of tissue anesthetic concentrations the hypothesis that long-term elimination of anesthetic from tissue is a function of tissue/blood partitioning. Thus, in accordance with current theory, our data indicate that volatile anesthetic tissue partition coefficients are good predictors of the long-term elimination kinetics of these drugs.

One possible confounding factor in the interpretation of the data is that we did not attempt to control for the differential effects of the two anesthetics on circulatory and ventilatory function. It is, however, unlikely that these factors had significant differential effects on anesthetic elimination that would dramatically skew the data and alter its interpretation. This is because the effects of both drugs on ventilation and cardiac output are similar in several mammalian species (10–14).

Although it is difficult to extrapolate results of anesthetic studies done in animal models to humans, the similarity of anesthetic partition coefficients in rats and humans (7) suggests that the relative anesthetic elimination kinetics might be similar in humans and animals. The greatest differences between the elimination kinetics in rats and humans are related to the absolute magnitudes of the rates of elimination. Rates of anesthetic elimination are slower in humans because of their relatively smaller ratio between ventilation and body mass and because in humans adipose tissue constitutes a larger percentage of total body weight. In fact, the predicted time constant of halothane elimination from adipose tissue in humans (45 h) (8) is approximately 10 times that which we measure in the rat. Some differences in the relative elimination rates of halothane and sevoflurane might also be expected on the basis of differing physiologic effects of these drugs on total cardiac output, distribution of cardiac output, and ventilation in the two different species. However, these differences should be small based on data that show that the effects of these anesthetics on ventilation and cardiovascular physiology are similar in several mammalian species (10–14).

In conclusion, our data suggest that the potential for postoperative psychomotor impairment caused by residual subanesthetic concentrations of anesthetic in tissue might be similar for halothane and sevoflurane in humans.

References

1. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: a new inhalational anesthetic agent. Anesth Analg 1975;54:758–65.
2. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 1981;54:100–6.
3. Fujii K, Morio M, Kikuchi H, et al. Pharmacokinetic study on excretion of inorganic fluoride ion, a metabolite of sevoflurane. Hiroshima J Med Sci 1986;36:89–92.
4. Eger EI II, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. Anesth Analg 1987;66:977–82.
5. Cook TL, Smith M, Starkweather JA, Winter PM, Eger EI II. Behavioral effects of trace and subanesthetic halothane and nitrous oxide in man. Anesthesiology 1978;49:419–24.
6. Cook TL, Smith M, Winter PM, Starkweather JA, Eger EI II.

Effect of subanesthetic concentrations of enflurane and halothane on human behavior. Anesth Analg 1978;57:434–40.

7. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 1989;69:370–3.
8. Eger EI II. Anesthetic uptake and action. 1st ed. Baltimore: Williams & Wilkins, 1974:77–97.
9. Stern RC, Weiss CI, Steinbach JH, Evers AS. Isoflurane uptake and elimination is delayed by absorption of anesthetic by the Scimed membrane oxygenator. Anesth Analg 1989;69:657–62.
10. Doi M, Ikeda K. Postanesthetic respiratory depression in humans: a comparison of sevoflurane, isoflurane and halothane. J Anesth 1987;1:137–42.
11. Doi M, Ikeda K. Respiratory effects of sevoflurane. Anesth Analg 1987;66:241–4.
12. Kazama T, Ikeda K. The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. J Anesth 1988;2:63–8.
13. Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. J Pharmacol Exp Ther 1984;231:640–8.
14. Litt L, Gonzalez-Mendez R, James TL, et al. An in vivo study of halothane uptake and elimination in the rat brain with fluorine nuclear magnetic resonance spectroscopy. Anesthesiology 1987;67:161–8.

Resistance to Atracurium-Induced Neuromuscular Blockade in Patients With Intractable Seizure Disorders Treated With Anticonvulsants

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TEMPELHOFF R, MODICA PA, JELLISH WS, SPITZNAGEL EL. Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. Anesth Analg 1990;71:665–9.

Previous studies have demonstrated that, with the exception of atracurium, resistance to the neuromuscular blocking effects of various muscle relaxants develops in patients receiving anticonvulsant therapy. We studied the effects of 0.5 mg/kg IV atracurium in 53 neurosurgical patients: 21 nonepileptic patients receiving no anticonvulsant therapy (MED = 0); 14 epileptic patients treated with carbamazepine for years (MED = 1); and 18 epileptic patients treated with carbamazepine plus either phenytoin or valproic acid for years (MED = 2). The evoked compound electromyogram of the adductor pollicis brevis was recorded, and results were analyzed using analysis of covariance, with weight and age as covariables. The onset time was not significantly different among the three groups. Times for recovery of baseline and train-of-four responses to stimuli were significantly shorter in the MED = 1 and MED = 2 groups than in control patients (MED = 0). The recovery index (time between 25% and 75% recovery of baseline electromyogram values) was progressively shorter in the three groups (MED = 0: 8.02 min; MED = 1: 5.93 min; MED = 2: 1.96 min; $P < 0.001$). This study demonstrates that atracurium, when used on epileptic patients requiring long-term (that is, years of) anticonvulsant therapy, has a shorter duration of action than when used in nonepileptic patients.

Key Words: NEUROMUSCULAR RELAXANTS, ATRACURIUM. COMPLICATIONS, EPILEPSY—atracurium.

Patients receiving one or more anticonvulsant medications, usually for the treatment of seizure disorders, are most infrequently encountered during anesthetic practice. Recent studies have demonstrated a higher requirement for fentanyl during anesthesia in this type of patient and a resistance to the neuromuscular blocking effects of metocurine, pancuronium, and vecuronium in subjects treated with anticonvulsants (1–7). However, none of these studies was able to demonstrate similar findings for atracurium, an intermediate-acting nondepolarizing muscle relaxant (4,6). As anesthesiologists regularly involved in the care of patients undergoing surgery for epilepsy, we have often noted that these individuals appear to be resistant to the recommended dosage of atracurium. Based on this clinical impression, we designed a study to determine whether epileptic patients on long-term anticonvulsant therapy have an altered requirement for atracurium-induced neuromuscular blockade.

Materials and Methods

After approval of the study protocol by the Institutional Review Board of Washington University School of Medicine, 53 consenting patients between the ages of 16 and 60 yr were studied. Patients with a history of significant renal, hepatic, metabolic, or cardiopulmonary disease (including arterial hypertension) were excluded from the study, as were patients with known ethanol or narcotic abuse and those with signs

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Presented in part at the 1989 Annual Meeting of the International Anesthesia Research Society.

Received from the Departments of Anesthesiology, Neurological Surgery, Mathematics, and Biostatistics, Washington University School of Medicine, St. Louis, Missouri. Accepted for publication August 2, 1990.

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of increased intracranial pressure. Patients taking drugs thought to affect the neuromuscular junction were also excluded. All study patients were within 30% of ideal body weight. A control group consisted of 21 otherwise healthy patients undergoing various types of craniotomies (e.g., for tumor, arteriovenous malformation, cerebrospinal fluid leak) who had never received anticonvulsant therapy. The remaining 32 patients had epilepsy with intractable seizure disorders, were undergoing craniotomy for seizure focus excision, and had been treated for years with various anticonvulsant regimens. The plasma levels of each anticonvulsant used were in the therapeutic range the day before surgery.

Each patient was premedicated with 150 mg ranitidine and 10 mg metoclopramide, both given orally, 1–2 h before surgery. On arrival in the operating room and throughout anesthesia, all patients were monitored with an electrocardiogram, blood pressure cuff (Dinamap), pulse oximeter, esophageal temperature probe with stethoscope, and mass spectrometer. In addition, an intraarterial catheter was inserted in all cases for direct measurement of blood pressure and arterial blood gas tensions. Tidal volume and respiratory rate were controlled to maintain end-tidal CO_2 between 25 and 30 mm Hg. Heating pads and a cascade humidifier were used to maintain esophageal temperature above 35°C.

Anesthesia was induced with 4–6 mg/kg intravenous (IV) thiopental and 3–10 μg/kg IV fentanyl. After facilitation of tracheal intubation with 0.5 mg/kg IV atracurium, anesthesia was maintained with 70% nitrous oxide (N_2O) in oxygen, 0.2%–0.3% end-tidal isoflurane, and fentanyl infusion (2–7 $\mu g \cdot kg^{-1} \cdot h^{-1}$). To avoid a possible drug interaction with atracurium, IV infusion of 10 mg/kg vancomycin was begun only after completion of data collection.

Neuromuscular transmission was monitored with a Puritan-Bennett/Datex Neuromuscular Transmission Monitor (NMT 221). This monitor was connected to the patient by five disposable surface electrodes as follows: two electrodes were used to stimulate indirectly the ulnar nerve at the wrist, while another two electrodes measured the resulting evoked compound electromyogram (EMG) of the adductor pollicis brevis muscle. The remaining (fifth) electrode served as a ground. The NMT 221 searches for the stimulus current (0–70 mA) needed to activate the fibers of the adductor pollicis brevis muscle. When found, this maximal current is then increased by 20%; the resulting current is the supramaximal stimulus. The NMT 221 then delivers a train-of-four square-wave (100 μs width) supramaximal impulse at 2.0 Hertz. This train-of-four is repeated every 20 s with the NMT 221 measuring the T-1% (twitch height) and TR% (train-of-four ratio) values where T-1% = (first EMG response/baseline EMG) × 100, and TR% = (fourth EMG response/first EMG response) × 100. These parameters were recorded on a printer. To minimize movement-induced changes in twitch responses, the patient's hand was carefully secured to a padded board.

Immediately after induction of anesthesia, the control EMG was recorded for 3 min to establish a stable baseline. Soon thereafter, a single bolus of 0.5 mg/kg IV atracurium was administered. The time in seconds from injection to the peak reduction of the EMG signal was recorded as the onset time. The times in minutes for recovery of T-1 to 25%, 50%, 75%, and 90% of baseline EMG levels were recorded, as were the times for recovery of TR to 25%, 50%, 75%, and 95% of baseline. In addition, we also measured the recovery index as the time from 25% to 75% recovery of the baseline EMG response. After completion of data collection, the 53 patients were retrospectively divided into the following medication (MED) groups based on the number of anticonvulsant(s) each was receiving (if any): MED = 0: 21 nonepileptic control patients who had never received anticonvulsant therapy; MED = 1: 14 epileptic patients in whom a therapeutic level of carbamazepine was documented before surgery; and MED = 2: 18 epileptic patients in whom therapeutic levels of carbamazepine plus either phenytoin or valproic acid were documented before surgery.

The EMG findings of the three medication groups were compared using analysis of covariance with age and weight as covariables; a $P < 0.05$ was considered statistically significant. The data were also analyzed using analysis of covariance for nonlinearity between the medication groups to ascertain statistical significance for an effect beyond a linear dose-response.

Results

The EMG response to the intubating dose of 0.5 mg/kg IV atracurium in the three MED groups is shown in Tables 1 and 2. All patients responded with at least a 95% depression in their baseline EMG; no significant difference in onset time was demonstrated between the three MED groups. In contrast, the patients in the MED = 1 and MED = 2 groups had significantly shorter times to recovery for T-1 at 25%, 50%, 75%, and 90% (Table 1), and for TR at 25%, 50%, 75%, and 95% (Table 2), when each group was compared with control (MED = 0) patients ($P < 0.001$). The same finding was also true for the recov-

Table 1. Onset Times and Times to Recovery of Twitch Height in the Three Groups (n = 53) After 0.5 mg/kg IV Atracurium

	Anticonvulsant medication groups		
	MED = 0 (n = 21)	MED = 1 (n = 14)	MED = 2 (n = 18)
Onset time (s)	184 ± 20.05	179 ± 23.48	220 ± 20.58
T-1 25% (min)^{a}	27.48 ± 6.65	14.21 ± 3.10^{b}	7.56 ± 3.14^{b,c}
T-1 50% (min)^{a}	32.98 ± 6.99	16.79 ± 3.26^{b}	8.40 ± 3.31^{b,c}
T-1 75% (min)^{a}	36.45 ± 8.46	19.98 ± 3.95^{b}	10.10 ± 4.01^{b,c}
T-1 90% (min)^{a}	38.76 ± 9.26	22.46 ± 4.3^{b}	11.78 ± 4.3^{b,c}

MED = 0, nonepileptic patients receiving no anticonvulsant therapy; MED = 1, epileptic patients treated with carbamazepine for years; and MED = 2, epileptic patients treated with carbamazepine plus either phenytoin or valproic acid for years.

Data analyzed by analysis of covariance. All values are expressed as least-square mean ± SE.

[a] These values refer to time for recovery of twitch height to 25%, 50%, 75%, and 90% of baseline electromyogram levels.

[b] Significantly different from control (MED = 0) group ($P < 0.001$).

[c] Significantly different from MED = 1 group ($P < 0.001$).

Table 2. Times to Recovery of Train-of-Four Ratio in the Three Groups After 0.5 mg/kg IV Atracurium

	Anticonvulsant medication groups		
	MED = 0^{a}	MED = 1	MED = 2
TR 25% (min)^{b}	33.70 ± 6.58	18.08 ± 3.07^{c}	6.52 ± 3.12^{c,d}
TR 50% (min)^{b}	41.10 ± 6.64	20.00 ± 3.09^{c}	7.98 ± 3.15^{c,d}
TR 75% (min)^{b}	46.58 ± 6.80	21.45 ± 3.17^{c}	8.46 ± 3.22^{c,d}
TR 95% (min)^{b}	50.64 ± 7.29	23.89 ± 3.40^{c}	9.76 ± 3.45^{c,d}

Data analyzed by analysis of covariance. All values are expressed as least-square mean ± SE.

[a] These abbreviations as in Table 1.

[b] These values refer to time for recovery of train-of-four ratio to 25%, 50%, 75%, and 95% of baseline levels.

[c] Significantly different from control (MED = 0) group ($P < 0.001$).

[d] Significantly different from MED = 1 group ($P < 0.001$).

ery index (Figure 1), when the MED = 1 and MED = 2 groups were each compared with the control (MED = 0) group (MED = 0: 8.02 min; MED = 1: 5.93 min; MED = 2: 1.96 min, $P < 0.001$). In addition, intergroup comparisons of the above recovery parameters (T-1%, TR%, and recovery index) also revealed significant differences between the MED = 2 and MED = 1 groups ($P < 0.001$). Analysis of covariance and a test for nonlinearity in the different MED groups also demonstrated that there was evidence for a direct inverse relationship between the number of anticonvulsants the patient was receiving and the time to recovery from atracurium-induced neuromuscular blockade. There was no evidence of an effect beyond a linear relationship.

Discussion

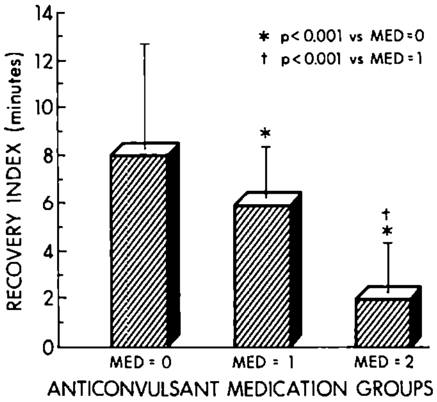

Figure 1. Recovery index, defined as the time between 25% and 75% recovery of the twitch height (T-1%) in the three medication (MED) groups after 0.5 mg/kg IV atracurium.

This study was designed to determine the recovery time from single-dose (0.5 mg/kg IV) atracurium-induced neuromuscular blockade in patients undergoing craniotomies, regardless of their medication or neurological history. Our results demonstrated that epileptic patients chronically treated with one or more anticonvulsants had significantly shorter times to recovery from atracurium. Furthermore, there seems to be a dose-effect relationship between the number of anticonvulsants received and a decreased time to recovery from atracurium-induced neuromuscular blockade (Figure 1). This does not imply that a patient receiving two different types of anticonvulsants experiences twice the antiseizure effect as someone receiving only one drug. It is impossible to quantify the level of additional antiseizure effect in patients treated with two different types of anticonvulsants when compared to someone receiving only one drug. However, we can assume that patients treated with therapeutic levels of two anticonvulsants are receiving a greater amount of medication compared with those treated with only one medication, and that there is a direct relationship between the amount of medication received and a shorter time to recovery from atracurium.

Previous studies have already demonstrated that patients receiving anticonvulsant therapy require increased amounts of narcotics, long-acting nondepolarizing muscle relaxants, and vecuronium (1–7). For muscle relaxants, this resistance is characterized as either an increased hourly requirement of relaxant or shorter recovery times after bolus administration. Although hepatic enzyme induction and/or pharmacodynamic alterations due to concomitant anticonvulsant therapy are suspected as possible causes, neither of these mechanisms alone can totally explain the increased resistance to muscle relaxants demonstrated in these patients (1,8). Various biophysiologic mechanisms have been proposed to explain this resistance including: increased endplate anticholinesterase activity; alteration in sensitivity to acetylcholine at the receptor site; and possibly an increased number of acetylcholine receptors. Alderdice and Trommer (9) found that carbamazepine depresses postjunctional sensitivity to the release of acetylcholine, producing a dose-related inhibition of endplate potential. In addition, carbamazepine inhibits transmitter release by decreasing quantal content of acetylcholine (9). Phenytoin also reduces the amplitude of endplate potentials due to both a reduction in quantal content and a decrease in the amplitude of the voltage response to acetylcholine quanta (10,11). On the basis of these studies, it is hypothesized that anticonvulsants depress neuromuscular transmission by reducing the amount of acetylcholine secreted in response to an action potential, thereby creating a state of chemical denervation at the motor endplate. This may cause either an increase in number and/or an increase in sensitivity of the acetylcholine receptor. A continuous insufficiency in acetylcholine at the neuromuscular junction could then result in upregulation of receptors and lead to a state of receptor hypersensitivity such that the effect after subsequent exposure to nondepolarizing muscle relaxants would be diminished.

Compared with the other clinically available nondepolarizing muscle relaxants, atracurium has a distinctly different metabolic pathway, utilizing Hoffman elimination and ester hydrolysis without renal or hepatic involvement (12). Ornstein et al. (4) studied the recovery time after single-dose (0.5 mg/kg IV) atracurium-induced neuromuscular blockade in patients previously treated for at least 7 days with phenytoin. They found no significant differences in the T-1% level of recovery or in the recovery index between the control group and the patients receiving phenytoin. These investigators concluded that atracurium-induced neuromuscular blockade was not affected by concomitant anticonvulsant therapy. To explain their finding, they suggested that, compared with other nondepolarizing muscle relaxants, atracurium may be more tightly bound to the neuromuscular junction and therefore less susceptible to the competitive antagonism of anticonvulsants. Their results appear to contradict our findings, but a major difference in patient populations may have contributed to these conflicting results. In our study, the 32 patients being treated with anticonvulsants had intractable seizure disorders that were poorly controlled by medical therapy, whereas Ornstein et al. studied patients receiving phenytoin for either recent onset of seizure or prophylaxis. Furthermore, the duration of anticonvulsant therapy was another important difference, as our epileptic patients have been on carbamazepine, phenytoin, and/or valproic acid for years, whereas their study patients had a minimum of 7 days of phenytoin therapy before various neurosurgical procedures. In another study, Ebrahim et al. (6) also showed no significant difference in the T-1% recovery and the recovery index between a control group and patients being treated with carbamazepine after a single dose of 0.5 mg/kg IV atracurium. Again, their study population did not consist entirely of patients with seizure disorders on long-term anticonvulsant therapy.

Our results demonstrate that recovery from atracurium-induced neuromuscular blockade is shortened in patients with seizure disorders receiving long-term (years of) anticonvulsant therapy. Because of differences in the patient population studied, our findings may not contradict those reported by Ornstein et al. and Ebrahim et al. In view of the conflicting results concerning recovery from atracurium-induced neuromuscular blockade in patients on anticonvulsants, we can only suggest that the duration of therapy and the number of anticonvulsants received play an important role in creating an increased resistance to atracurium. Also, does the nature of the epileptic disease itself play a role in altering the neuromuscular endplate and therefore shortening the duration of atracurium-induced neuromuscular blockade? Approximately 60,000 patients suffering from intractable seizures are treated conservatively (i.e., pharmacologically), usually with a combination of several anticonvulsants (13). Few of them undergo seizure surgery, but a great number of them will require surgery for other reasons. Their resistance to atracurium and other nondepolarizing muscle relaxants (1–6), along with their high requirements for fentanyl (7), are important factors in the routine anesthetic management of epileptic patients on long-term anticonvulsant therapy. Only further pharmacokinetic, neurobiologic, and electrophysiologic studies in epileptic patients will allow us to understand this phenomenon better.

References

1. Ornstein E, Matteo RS, Young WL, Diaz J. Resistance to metocurine-induced neuromuscular blockade in patients receiving phenytoin. Anesthesiology 1985;63:294–8.
2. Messick JM, Maass L, Faust R, Cucchiara RF. Duration of pancuronium neuromuscular blockade in patients taking anticonvulsant medication. Anesth Analg 1982;61:203–4.
3. Roth S, Ebrahim ZY. Resistance to pancuronium in patients receiving carbamazepine. Anesthesiology 1987;66:691–3.
4. Ornstein E, Matteo RS, Schwartz AE, Silverberg PA, Young WL, Diaz J. The effect of phenytoin on the magnitude and

duration of neuromuscular block following atracurium or vecuronium. Anesthesiology 1987;67:191–6.

5. Bulkey R, Ebrahim Z, Roth S, DeBoer G, Run S. Resistance to vecuronium in patients receiving carbamazepine (abstract). Anesthesiology 1987;67:A345.
6. Ebrahim Z, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium or vecuronium (abstract). Anesth Analg 1988;67:S55.
7. Tempelhoff R, Modica PA, Spitznagel EL. Anticonvulsant therapy increases fentanyl requirements during anaesthesia for craniotomy. Can J Anaesth 1990;37:327–32.
8. Liberman BA, Norman P, Hardy BG. Pancuronium-phenytoin interaction: a case of decreased duration of neuromuscular blockade. Int J Clin Pharmacol 1988;26:371–4.
9. Alderdice MT, Trommer BA. Differential effects of the anticonvulsants phenobarbital, Ethosuximide and carbamazepine on neuromuscular transmission. J Pharmacol Exp Ther 1980;215: 92–6.
10. Gage PW, Lonergan M, Torda TA. Presynaptic and postsynaptic depressant effects of phenytoin sodium at the neuromuscular junction. Br J Pharmacol 1980;69:119–21.
11. Yaari Y, Pincus JH, Argov Z. Depression of synaptic transmission by diphenylhydantoin. Ann Neurol 1977;1:334–8.
12. Fisher DM, Canfell PC, Fahey MR, et al. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis *versus* organ-based elimination. Anesthesiology 1986;65:6–12.
13. Goldring S, Gregorie EM, Tempelhoff R. Surgery of epilepsy. In: Rob, Smith, eds. Operative surgery: neurosurgery. London: Butterworths, 1989:427–42.

Lidocaine Local Anesthesia for Arthroscopic Knee Surgery

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DAHL MR, DASTA JF, ZUELZER W, McSWEENEY TD. Lidocaine local anesthesia for arthroscopic knee surgery. Anesth Analg 1990;71:670–4.

Forty-five patients were evaluated during knee arthroscopy performed using local anesthesia produced by lidocaine with epinephrine to determine the dose-response relationship for operative analgesia. Serum lidocaine concentrations were also measured. Patients were randomized prospectively to receive 20 mL of 0.5%, 1.0%, or 1.5% lidocaine with epinephrine intraarticularly. Intraoperative discomfort was measured by verbal response on an 11-point linear pain scale. Pain scores were significantly higher in patients receiving 0.5% lidocaine during the first 45 min of surgery ($P = 0.03$). After 45 min, pain scores continued to be higher in the 0.5% lidocaine group than in the 1.0% or 1.5% groups, but the differences were not statistically significant. Ninety-four percent of patients in the 1.5% lidocaine group were willing to repeat this anesthetic technique for surgery compared with 83% of those in the 1.0% lidocaine group and 75% of those in the 0.5% lidocaine group ($P > 0.05$). The duration of postoperative analgesia was similar in all groups. Serum lidocaine concentrations before and 15, 30, 60, and 120 min after instillation of lidocaine were highest in the 1.5% lidocaine group with a peak concentration of 278 ng/mL. No patient had symptoms of lidocaine toxicity. We recommend that lidocaine concentrations of 1.0% or 1.5% be used when 20 mL is instilled intraarticularly for knee arthroscopy based on patient comfort and absence of lidocaine toxicity.

Key Words: ANESTHESIA, ORTHOPEDIC—knee arthroscopy with lidocaine. ANESTHETIC TECHNIQUES, LOCAL—knee arthroscopy.

Periarticular infiltration and intraarticular (IA) instillation of local anesthetics is a suitable method of anesthesia for arthroscopic knee surgery and may be an alternative to regional or general anesthesia (1–3). Several methods for producing IA anesthesia have been described for knee arthroscopy that differ in volume, concentration, and type of local anesthetic, use of adjuvant epinephrine, and method of local anesthetic instillation (1–10). Although all regimens have a high success rate, dose requirements have been reported only for bupivacaine (5). Lidocaine has been described for use alone or in combination with bupivacaine, but dose requirements have not been reported (2,6–8). The purpose of this study was to determine the dose-response relationship for lidocaine and to measure serum lidocaine concentrations after extraarticular and IA administration in patients undergoing knee arthroscopy.

Methods

Forty-five outpatients (ASA physical status I or II) scheduled for arthroscopic knee surgery participated in this institutionally approved, randomized, double-blind study. Written informed consent was obtained before patients entered the study.

All patients were offered inhalation of nitrous oxide and oxygen (50/50 mixture) by mask before lidocaine injection; no other premedication was administered. With the patient supine, the operative knee was shaved, the skin was cleansed with povidone-iodine solution, and the knee draped. In all patients, 20 mL of 0.5% lidocaine (Astra Pharmaceutical Products Inc., Westborough, Mass.) with freshly added epinephrine (Elkins-Sinn Inc., Cherry Hill, N.J.) (1:200,000) was injected into the skin, subcutaneous tissue, and capsule in three peripatellar portals. Entry portals were located medial to the patellar tendon, lateral to the patellar tendon, and off the superolateral corner of the patella (1). The IA injec-

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This work was performed at the Ohio State University Hospitals in Columbus, Ohio.

Presented at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from the Departments of Anesthesiology and Surgery and the College of Pharmacy, The Ohio State University, Columbus, Ohio. Accepted for publication August 3, 1990.

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tion was made through an anesthetized skin portal. Patients were randomized to receive 20 mL intraarticularly of 0.5%, 1.0%, or 1.5% preservative-free lidocaine with freshly added epinephrine (1:200,000). Spread of IA lidocaine was encouraged by flexion and extension of the knee joint.

Throughout surgery the joint was flushed continuously by gravity with lactated Ringer's solution. At the end of surgery, the arthroscope (4-mm Storz, 30-degree lens) and surgical instruments were removed, and the joint was flushed with copious amounts of lactated Ringer's solution. Patients returned to the ambulatory surgery unit until discharge.

Pain was measured by verbal response to an 11-point pain scale, consisting of a 10-cm horizontal line labeled "no pain" at 0 and "agonizing pain" at 10. The line was divided into 11 equal segments and numbered. Patients were shown the pain scale before each measurement. If a pain score greater than 3 was reported and not relieved by repositioning the leg or injecting lidocaine into the skin, patients were first offered inhalation of nitrous oxide and oxygen (50/50 or 60/40 mixture by mask). If the pain was not diminished after nitrous oxide and oxygen, patients were offered intravenous fentanyl (50 μg); likewise, if the pain was not diminished after nitrous oxide and oxygen and fentanyl, patients were offered general anesthesia. Pain was measured after IA injection and arthroscope insertion and at 15-min intervals during surgery. Patients were also asked to record the time and pain score when the first postoperative oral analgesic was taken and the highest pain score during the night after surgery. Patients were later interviewed by telephone.

Venous blood was collected immediately before extraarticular injection and 15, 30, 60, and 120 min after the IA lidocaine injection. No patient received supplemental injections of lidocaine. The blood was centrifuged and the serum harvested and stored at −80°C. Lidocaine concentrations were determined in duplicate by gas-liquid chromatography with a nitrogen phosphorous detector, with a sensitivity of 5 ng/mL and a coefficient of variation less than 10% (11).

Statistical analyses were performed using Statistical Analysis System (SAS, version 5.11, 1988) computer programs (12,13). Patient characteristics were compared using one-way analysis of variance. The Mantel–Haenszel χ^2-test was used to compare gender, the type of surgery, and patient data as appropriate. The Kruskal–Wallis rank sum test was used to compare washout times and the duration of surgery and postoperative analgesia. A nonparametric repeated measures analysis of variance test compared pain scores (14). Differences were considered statistically significant if the exact probability test value was less than 0.05.

Table 1. Patient and Operative Data

	Groups		
	0.5%[a]	1.0%	1.5%
Age (yr)	37 ± 16	36 ± 12	28 ± 7
Weight (kg)	82 ± 12	78 ± 14	74 ± 12
Gender (M/F)	8/4	10/5	11/5
Washout (min)	28 ± 8	28 ± 8	29 ± 7
Surgery duration (min)	73 ± 23	69 ± 20	67 ± 26
Operative/diagnostic	10/2	14/1	14/2

Values listed are mean ± SD, except for gender and surgical procedure, which are patient counts. Surgical procedures are grouped as operative (resection or repair of intraarticular tissue) and diagnostic (visualization with or without biopsy). Differences between groups were not statistically significant.

[a] These values refer to the intraarticular lidocaine concentration administered.

Results

The groups were similar with respect to age, weight, and gender. The duration of IA lidocaine (listed as washout), duration of surgery, and type of surgical procedure were not statistically different between groups (Table 1).

The 0.5% lidocaine group had significantly higher pain scores through the first 45 min of surgery than either the 1.0% or 1.5% lidocaine groups (Figure 1). Pain scores through the last intraoperative measurement were not statistically different among groups. Power analysis of combined pain scores from incision to 30 min ($n = 43$) and from incision to 45 min ($n = 38$) revealed that our sample size and variability was such that we could detect group differences with 0.89 and 0.73 power, respectively (α error of 0.05).

More patients in the 1.5% lidocaine group were given nitrous oxide and oxygen before lidocaine injection than patients in either the 0.5% or 1.0% group. The number of patients in each group that inhaled nitrous oxide and oxygen intraoperatively was similar (Table 2). Only one of the patients who reported a pain score of 3 or less intraoperatively requested inhalation of nitrous oxide and oxygen. The duration of postoperative analgesia was similar among groups (Table 2). Eighty-five percent of all patients interviewed by telephone said they would be willing to repeat this anesthetic technique. The number of patients willing to repeat this anesthetic technique was greatest in the 1.5% lidocaine group (94%),

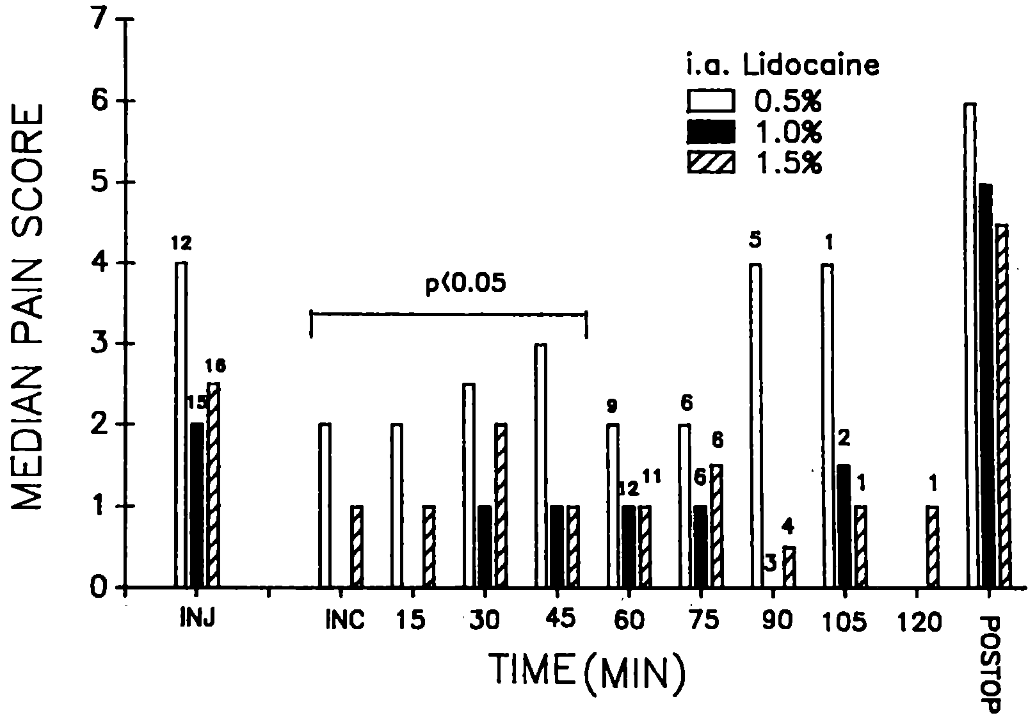

Figure 1. Median pain scores plotted by group at each measurement period. Pain scores are significantly higher in the 0.5% lidocaine group through 45 min of surgery. The number of patients remaining at each time period is listed above the bar. INJ, injection; INC, incision; and POSTOP, postoperative.

Table 2. Clinical Summary

	Groups		
	0.5%[a] (n = 12)	1.0% (n = 15)	1.5% (n = 16)
N_2O before lidocaine (n)	2	2	6
Intraoperative N_2O (n)	6	3	5
Duration of analgesia (h)	6.0 ± 3.3	5.9 ± 2.9	5.5 ± 2.3
Repeat local anesthesia (%)	75	83	94

The duration of analgesia was the time from intraarticular injection until the onset of pain after surgery. Patient willingness to repeat local anesthesia for this procedure is listed as "repeat local anesthesia." One patient from the 0.5% and three from the 1.0% lidocaine group were lost to follow-up. There were no statistically significant differences between groups.

[a] These values refer to the intraarticular lidocaine concentration administered.

but the differences among the three groups were not statistically significant (Table 2). Two patients in the 0.5% lidocaine group required general anesthesia because of knee pain. No patient required pneumatic tourniquet inflation for intraoperative control of bleeding in the knee joint. The surgeon reported satisfactory visualization and access to IA structures.

Serum lidocaine concentrations in 17 patients ranged from undetectable to 278 ng/mL. Peak concentrations occurred 60 and 120 min after IA injection. The 1.5% lidocaine group had the highest concentrations (Figure 2). No patient reported symptoms of lidocaine toxicity.

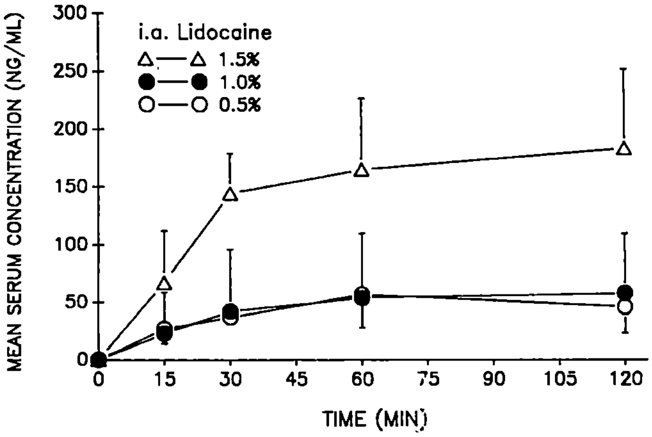

Figure 2. Venous serum concentrations of lidocaine versus time after IA lidocaine instillation.

Discussion

In the present study the level of patient satisfaction with local anesthesia was similar to other reports and comparable to different anesthetic techniques (3). Eriksson et al. (3) surveyed 278 patients who had arthroscopic knee surgery using spinal, general, or local anesthesia. Ninety-seven percent of patients given general anesthesia reported satisfaction, as compared with 77% of patients having local anesthesia and 64% of those given spinal anesthesia. In 11% the spinal anesthetics were not sufficient and general anesthesia was required. In the present study 14% of patients in the 0.5% lidocaine group were given general anesthesia because of insufficient anesthesia.

The desire for an adequate duration of intraoperative analgesia and prolonged postoperative analgesia may have prompted other investigators to combine lidocaine with a longer acting local anesthetic, such as bupivacaine (2,7,8), or to irrigate the joint intraoperatively with a dilute lidocaine solution (6). The results of the present study suggest that a single IA dose of lidocaine with epinephrine provides satisfactory analgesia for arthroscopic procedures on the knee. Both 1.0% and 1.5% lidocaine provide significantly better analgesia than 0.5% lidocaine through 45 min of surgery. The trend in pain scores remained constant after 45 min, but differences were not statistically significant. This may be due in part to the fact that fewer subjects remained in the analysis. The duration of postoperative analgesia, however, was not prolonged with the higher concentrations of lidocaine, perhaps because similar amounts of lidocaine remain in the knee after joint irrigation, regardless of the initial dose, or because the maximal effect occurs with the lowest concentration studied.

The techniques described for IA instillation of local anesthetic include an initial injection of local anesthetic with subsequent washout by continuous irrigation, either with an isotonic crystalloid solution (2,7,8) or with a dilute concentration of local anesthetic (3,4,6,10). Other authors anesthetize the skin portals and continuously irrigate the joint with a dilute solution of local anesthetic without an initial IA injection (4,10). The joint can be irrigated by gravity infusion (3,6,7,9) or by a pressure-controlled inflow device (1,4,8,10). Pressurized irrigation is thought to decrease IA bleeding, to provide better joint distention, and to evacuate debris efficiently (8,10). However, periarticular extravasation has resulted in leg swelling (4,10) and systemic absorption of local anesthetic (10). In our study irrigation by gravity inflow provided satisfactory operative conditions (3,6,7,9) and functioned without complication.

The serum lidocaine concentrations in the 1.5% lidocaine group were higher than those in the 0.5% or 1.0% lidocaine groups. All lidocaine concentrations were at least an order of magnitude lower than those associated with systemic toxicity, which is usually greater than 5 μg/mL (15). Although we sampled blood for only 120 min, it is unlikely that further absorption of lidocaine would be significant because the joint was flushed with lactated Ringer's solution during and after surgery. Lidocaine concentrations in the present study are comparable to those reported by Massey et al. (6), who used a similar IA dose but then irrigated with a 0.2% lidocaine solution. Although absorption of extraarticular lidocaine contributed to the total venous concentration, the dose was constant for all three groups.

Epinephrine will slow local anesthetic absorption from the knee after periarticular and IA injection. Yoshiya et al. (7) reported mean venous lidocaine concentrations of 900–1000 ng/mL and a maximum value of 2400 ng/mL after administering an IA lidocaine and bupivacaine solution without epinephrine. A similar IA lidocaine dose with epinephrine in our study resulted in mean concentrations of 100–200 ng/mL and a maximum value of 278 ng/mL. Epinephrine also decreases serum concentrations of bupivacaine when injected into the knee (16). Epinephrine may act to decrease IA bleeding during surgery and to negate the need for tourniquet inflation. If tourniquet inflation is part of the surgical technique, a different anesthetic technique may be necessary.

In conclusion, arthroscopy of the knee under lidocaine local anesthesia can be performed in many patients who desire to remain awake. The frequent use of systemic analgesics intraoperatively, however, points out the need for an appropriate level of anesthesiological vigilance. We recommend the use of 1.0% or 1.5% lidocaine with epinephrine based on patient comfort intraoperatively and the absence of lidocaine toxicity in any of our patients.

The authors thank Cathy L. Chambers and Richard I. Cook, MD, for their help in the preparation of this manuscript.

References

1. McGuire DA, Forst JD, Floerchinger SL. Local anesthesia and arthroscopic surgery of the knee. Alaska Med 1986;28:20–4.
2. Ngo IV, Hamilton WG, Wichern WA, Andree RA. Local anesthesia with sedation for arthroscopic knee surgery of the knee: a report of 100 consecutive cases. Arthroscopy 1985;1: 237–41.
3. Eriksson E, Haggmark T, Saartok T, Sebik A, Ortengren B. Knee arthroscopy with local anesthesia in ambulatory patients. Orthopedics 1986;9:186–8.
4. Debruyne D, Moulin MA, Carmes C, Beguin JA, Locker B. Monitoring serum bupivacaine levels during arthroscopy. Eur J Clin Pharmacol 1985;27:733–5.
5. Gerber H, Censier K, Gacht AA, Romppainen J. Intra-articular absorption of bupivacaine during arthroscopy—comparison of 0.25%, 0.5% and 0.75% solution. Anesthesiology 1985;64: A217.

6. Massey T, Huang TL, Malinick R, Zell M. Serum lidocaine levels during arthroscopy using continuous irrigation with lidocaine. Clin Orthop 1988;229:182–4.
7. Yoshiya S, Kurosaka M, Hirohata K, Andrish JT. Knee arthroscopy using local anesthetic. Arthroscopy 1988;4:86–9.
8. Halperin N, Anatol A, Hirschberg E, Agasi M. Arthroscopy of the knee under local anesthesia and controlled pressure-irrigation. Clin Orthop 1978;134:176–9.
9. Meining RP, Holtgrewe JL, Wiedel JD, Christie DB, Kestin KJ. Plasma bupivacaine levels following single dose intraarticular instillation for arthroscopy. Am J Sports Med 1988;16:295–300.
10. Wedmark T, Lundh R. Arthroscopy under local anaesthesia using controlled pressure-irrigation with prilocaine. J Bone Joint Surg [Br] 1982;64:583–5.
11. Abernethy DR, Greenblatt DJ. Lidocaine determination in human plasma with application to single-dose pharmacokinetic studies. J Chromatogr 1982;232:180–5.
12. Ray AA, Sall JP, Saffer M. SAS user's guide: statistics. Cary, N.C.: SAS Institute Inc., 1982:139–200, 205–12, and 381–96.
13. Allen A, Council KA, Sall JP. SAS user's guide: basics. Cary, N.C.: SAS Institute Inc., 1982:527–32 and 575–86.
14. Tandon PK, Moeschberger ML. SAS Macros for nonparametric analysis of repeated measures designs, SAS Users Group, International. New Orleans: SAS Institute Inc., 1983:808–17.
15. Pieper JA, Rodman JH. Lidocaine. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics. Spokane, Wash.: Applied Therapeutics Inc., 1986:639–81.
16. Carnes RS, Butterworth IV, Poehling GS, Samuels MP. Safety and efficacy of intra-articular bupivacaine and epinephrine anesthesia for knee arthroscopy. Anesthesiology 1989;71:A729.

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1990;71:675–8

Esmolol Attenuates Cardiovascular Responses to Extubation

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Changes in heart rate and systolic blood pressure were measured during extubation and emergence from anesthesia in 40 ASA physical status I and II patients in a double-blind study to assess the effect of three doses of esmolol (1, 1.5, and 2 mg/kg) given as a bolus 2 min after reversal of neuromuscular blockade. Heart rate ($P < 0.01$), systolic blood pressure ($P < 0.02$), and rate-pressure product ($P < 0.01$) increased significantly during extubation of the control group. All doses of esmolol attenuated the increases in heart rate, but 1 mg/kg was insufficient to control the increase in systolic blood pressure. Doses of 1.5 and 2 mg/kg controlled both systolic blood pressure and heart rate, but the larger dose produced significant decreases in systolic blood pressure.

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol. ANESTHETIC TECHNIQUES, EXTUBATION—esmolol.

Numerous studies have reported an association of hypertension and tachycardia with laryngoscopy and tracheal intubation (1–4). Increases in blood pressure and heart rate (HR) at the end of anesthesia and during extubation are also common (5) and may cause dangerous increases in myocardial oxygen demand in patients with coronary artery disease (6,7). Acute increases in blood pressure may also be hazardous in patients who have undergone neurosurgical procedures.

Esmolol is an ultrashort-acting, highly cardioselective β-adrenergic receptor antagonist. Its rapid elimination is due to conversion to an inactive free acid metabolite by plasma esterases (8,9). The purpose of this study was to evaluate the effect of various doses of esmolol on cardiovascular responses to extubation.

Patients and Methods

After Institutional Review Board approval, 40 ASA physical status I and II patients, age range, 18–65 yr, who were scheduled for elective noncardiac surgery agreed to participate in the study. Patients were excluded if they had a history of bronchospasm or if they were currently taking cardiovascular or antihypertensive medications. The patients were randomly divided into four groups using random-number tables to assign a sealed envelope to each patient. Group 1 was the control group and was given a placebo; group 2 patients were given 1.0 mg/kg esmolol; group 3 patients were given 1.5 mg/kg esmolol; and group 4 patients were given 2.0 mg/kg esmolol.

All patients were premedicated with ranitidine (150 mg) and sodium citrate (30 mL) orally 1 h preoperatively. Before general anesthesia, three readings of HR and blood pressure were taken; the mean value was used as the baseline. Anesthesia was induced with 4–6 mg/kg thiopental and 0.15 μg/kg sufentanil. Vecuronium (0.1 mg/kg) was used for neuromuscular relaxation and given in 1-mg increments. Patients were ventilated to normocapnea with isoflurane in 70% nitrous oxide in oxygen to obtain end-tidal isoflurane concentrations of 0.2%–0.6%, as measured by mass spectrometry, according to patient response to surgery. A target of within 10% of normal systolic blood pressure (SBP) and HR was used to adjust the vaporizer setting. Incremental doses of 0.1 μg/kg sufentanil were given every 30 min. At the end of surgery, isoflurane and nitrous oxide were discon-

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Received from the Department of Anesthesiology, University of Texas Southwestern Medical Center, Dallas, Texas. Accepted for publication August 6, 1990.

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Table 1. Patient Characteristics for Each of the Four Groups

Characteristic	Group: Placebo	1 mg/kg esmolol	1.5 mg/kg esmolol	2 mg/kg esmolol
Age (yr)	32.9 ± 9.5	30.3 ± 8.5	37.1 ± 10.4	35.3 ± 8.8
No. of women	7	6	7	6
Weight (kg)	76 ± 17.7	69.1 ± 11.1	65.4 ± 11.1	68.9 ± 13.1
Baseline HR (beats/min)	72 ± 8.7	81 ± 17.1	73 ± 15.7	82 ± 19.7
Baseline SBP (mm Hg)	125 ± 12.0	130 ± 13.6	122 ± 18.4	125 ± 11.8
Duration of surgery (min)	98 ± 29.3	124 ± 95.5	103 ± 55.1	143 ± 72.0

HR, heart rate; SBP, systolic blood pressure.
All values are expressed as mean ± SD, except that for "No. of women."

tinued. When the end-tidal isoflurane concentration was 0.1%, 2.5 mg neostigmine and 0.5 mg glycopyrrolate were given over 30 s to reverse neuromuscular blockade. Two minutes later, esmolol or placebo was given intravenously over 30 s in 15 mL of saline. This had been prepared beforehand by an assistant using the sealed envelope, and its identity was unknown to the anesthesiologist. Extubation was performed when the patients could breathe spontaneously and open their eyes on command. In practice this was between 2 and 5 min after the injection of esmolol.

Blood pressure and HR were recorded every 3 min during anesthesia and every minute from the time of reversal; the same noninvasive blood pressure monitor (Dinamap) and printer was used for all patients.

Changes in HR and blood pressure between groups were compared and analyzed with Student's *t*-test and two-way analysis of variance with repeated measures on time. Changes in HR and SBP of greater than 20% were noted and analyzed by the χ^2 test. A P value less than 0.05 was accepted as significant.

Results

No statistical differences were found between any of the four groups for weight, age, sex, duration of anesthesia, resting SBP, or HR (Table 1). In addition there were no differences in the times for extubation between groups; all patients were extubated within 4 min of receiving esmolol or placebo.

During extubation in the control group HR and SBP increased significantly when compared to baseline levels ($P < 0.01$ and $P < 0.02$, respectively).

After treatment the number of patients in whom HR increased more than 20% was significantly greater in the control group than in all three esmolol groups ($P < 0.01$; Figure 1). Significantly more patients (all 10) in the control group had increases in HR of greater than 20% than did patients in the esmolol groups ($P < 0.05$), but the changes in HR were not significantly different between groups.

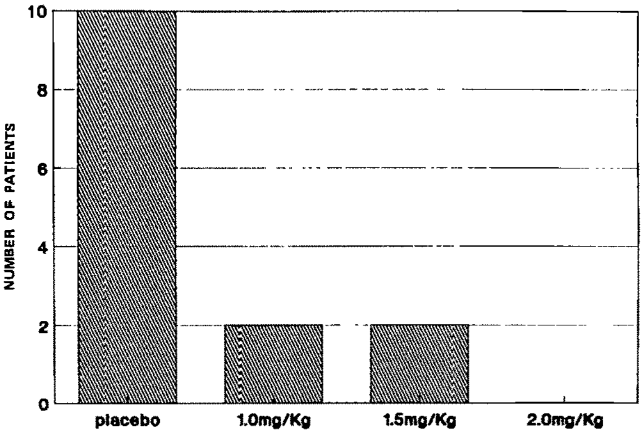

Figure 1. Number of patients who developed increases in HR of 20% or more upon extubation after placebo or esmolol (n = 10 for each group).

The number of patients in whom SBP increased more than 20% was significantly greater in the control group than in the 1.5- and 2.0-mg/kg esmolol groups ($P < 0.02$), but the difference between the control group and the 1.0-mg/kg group was not significant (Figure 2). A dose of 2.0 mg/kg was no more effective than 1.5 mg/kg in suppressing increases in SBP. The number of patients in the control and 1-mg/kg groups who had increases of 20% or more in the SBP was significantly greater ($P < 0.05$) than in the 1.5- and 2-mg/kg groups, which did not differ significantly with each other. Of the 10 patients in the control group, six had a maximal increase in SBP of 40% or more (seven had an SBP in excess of 150 mm Hg and two had an SBP in excess of 200 mm Hg). No patient in a group receiving esmolol had a maximal increase in SBP above 35%.

Two patients in the 1.5-mg/kg esmolol group and five patients in the 2-mg/kg group had decreases in SBP of more than 20%, compared with none in the

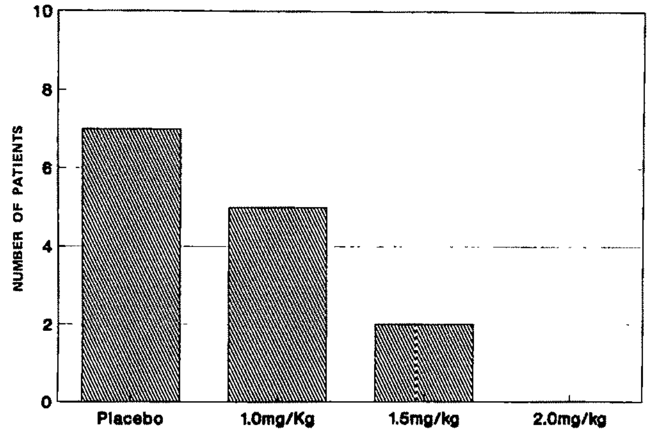

Figure 2. Number of patients who developed increases in SBP of 20% or more upon extubation after placebo or esmolol (n = 10 for each group).

control and 1.0-mg/kg groups. The difference was only significant for the 2-mg/kg group ($P < 0.05$).

Discussion

Cardiovascular changes such as hypertension and tachycardia during tracheal intubation are potentially detrimental to patients with ischemic heart disease (4,10). We have shown in this study that similar pressor responses and tachycardia can occur in healthy patients during emergence from anesthesia, and that these responses are easily blocked by a bolus dose of esmolol. An intravenous dose of 1.5 mg/kg is sufficient to produce attenuation without decreases in HR and SBP that may occur with a larger dose. Better control may be achieved by the use of repeated smaller doses, a continuous infusion of esmolol, or by use of a longer acting drug such as labetalol, although these methods are intrinsically more complex. A recent study of extubation in patients who had undergone craniotomy and were hypertensive on emergence showed that, although effective, labetalol tended to decrease HR postoperatively when compared with a continuous infusion of esmolol (11). In addition, esmolol is the most β_1-selective adrenergic blocker available (9) and may be less likely to provoke bronchospasm than labetalol (12).

Lidocaine has been used with apparent good effect to suppress not only the cardiovascular response to extubation but also the coughing associated with the presence of an endotracheal tube (5). However, the mechanism by which lidocaine works remains unclear. It may be caused by deepening of anesthesia or by local anesthesia of the airway. Neither of these effects is desirable at the conclusion of anesthesia.

Esmolol, with its rapid onset and extremely short duration of action ($t_{1/2}$ = 9 min) (9), would appear to be an ideal drug for preventing acute increases in HR and SBP. However, we would advise caution when using bolus doses of esmolol during extubation unless the patient has received atropine or glycopyrrolate (as part of the reversal of neuromuscular blockade) because tracheal stimulation in the presence of β-blockade may potentially produce profound bradycardia.

No patient in our study required treatment for hypotension, bradycardia, or significant arrhythmias. No side effects were observed in any patient, with the exception of one patient in the 1.5-mg/kg group, who complained of vivid dreams during recovery.

Several studies have shown that β-adrenergic blockade with esmolol can obtund the tachycardia and hypertension associated with endotracheal intubation (13–16). We have found only one published study investigating the effect of esmolol on the reflex cardiovascular response associated with extubation in the perioperative period, and this related specifically to craniotomy patients who were treated after the onset of hypertension (11).

In summary, we have shown that the increase in HR that occurs during extubation can be successfully attenuated by bolus injection of 1 mg/kg esmolol, although this dose is insufficient to effectively block increases in SBP. A larger dose of 1.5 mg/kg blocks the maximal increase in HR and controls SBP. Doses of 2 mg/kg produce significant (>20%) decreases in SBP without further attenuation of the pressor or HR responses. The use of esmolol before extubation may be beneficial in patients with ischemic heart disease and good left ventricular function, especially in the presence of borderline hypertension.

We would like to thank Du Pont Pharmaceuticals for their support and encouragement of this study. We would also like to thank Dr. D. McIntire and the Department of Academic Computing at the Southwestern Medical Center for their kind help with the statistical analysis of our data.

References

1. Forbes AM, Daley FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. Br J Anaesth 1970;42:618–24.
2. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during noncardiac surgical procedures in patients with coronary artery disease. Anesthesiology 1979;51:393–7.
3. Fox EJ, Sklar GS, Hill CH, Villanuava R, King BD. Complica-

tions related to endotracheal intubation. Anesthesiology 1977; 47:524–5.

4. Prys-Roberts C, Green LT, Meloche R, Föex P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 1971;43:531–46.
5. Bidwai AR, Bidwai VA, Rodgers CR, Stanley TH. Blood pressure and pulse-rate responses to endotracheal extubation with and without prior injection of lidocaine. Anesthesiology 1979;51:171–3.
6. Braunwald E. Control of myocardial oxygen consumption: anesthesiologic and clinical considerations. Am J Cardiol 1971; 27:416–32.
7. Kaplan JA, King SB. The precordial electrocardiographic lead (V5) in patients who have coronary artery disease. Anesthesiology 1976;45:570–4.
8. Zarozlinski J, Borgman RJ, O'Donnell JP, et al. Ultra-short acting beta blockers: a proposal for treatment of the critically ill patient. Life Sci 1982;31:899–907.
9. Gorczynski RJ, Shaffer JE, Lee RJ. Pharmacology of ASL-8052, a novel beta-adrenergic receptor antagonist with an ultrashort duration of action. J Cardiovasc Pharmacol 1983;5:668–77.
10. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
11. Muzzi DD, Black S, Losasso J, Cucchiara RF. Labetalol and esmolol in the control of hypertension after intracranial surgery. Anesth Analg 1990;70:68–71.
12. Inada E, Cullen DJ, Nemeskal AR, Teplick R. Effect of labetalol or lidocaine on the hemodynamic response to intubation: a controlled randomized double-blind study. J Clin Anesthesiol 1989;1:207–13.
13. Menkhaus PG, Reves JG, Kissin I, et al. Cardiovascular effects of esmolol in anesthetized humans. Anesth Analg 1985;64:327–34.
14. De Brunin NP, Croughwell N, Reves JG. Hemodynamic effects of esmolol in chronically beta blocked patients undergoing aortocoronary bypass surgery. Anesth Analg 1987;66: 137–41.
15. Liu PL, Gatt S, Gugino LD, Mallampati SR, Covino BJ. Esmolol for control of increases in heart rate and blood pressure during tracheal intubation after thiopentone and succinylcholine. Can Anaesth Soc J 1986;33:556–62.
16. Cucchiara RF, Benefiel DJ, Matteo RS, DeWood M, Albin MS. Evaluation of esmolol in controlling increases in heart rate and blood pressure during endotracheal intubation in patients undergoing carotid endarterectomy. Anesthesiology 1986;65: 528–31.

Fetal Heart Rate Variability After Epidural Fentanyl During Labor

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VISCOMI CM, HOOD DD, MELONE PJ, EISENACH JC. Fetal heart rate variability after epidural fentanyl during labor. Anesth Analg 1990;71:679–83.

The effects of epidural fentanyl on fetal heart rate (FHR) were examined in 39 parturients, 19 given 75 μg epidural fentanyl and 20 given normal saline in 5-mL volumes administered randomly after establishment of adequate epidural lidocaine analgesia. Fetal heart rate was measured 15 min before and 15 min after lidocaine epidural analgesia, and for 60 min at 5-min intervals after administration of epidural fentanyl/placebo. A perinatologist blinded to the injected epidural solution analyzed FHR tracings. Epidural injections of fentanyl and saline, when given during established epidural lidocaine analgesia, were associated with equal reductions in FHR variability and the frequency of FHR accelerations ($P < 0.003$). Neonatal outcome was also similar in both groups. The clinical significance, if any, of these moderate reductions in FHR during epidural lidocaine analgesia is unclear.

Key Words: ANESTHESIA, OBSTETRICAL—fetal heart rate. ANESTHETIC TECHNIQUES, EPIDURAL—fentanyl.

Epidural fentanyl is often utilized to supplement epidural local anesthetics for analgesia during labor. Possible benefits of supplementing epidural local anesthetics with fentanyl include better and more rapid onset of analgesia (1–3). When administered by continuous epidural infusion, combining fentanyl with dilute epidural local anesthetics produces analgesia equivalent to that produced by more concentrated local anesthetic solutions without fentanyl (4). In addition, dilute local anesthetic solutions mixed with fentanyl produce less motor block (4).

Maternal intravenous morphine, meperidine, and fentanyl decrease fetal heart rate (FHR) variability for up to 30 min (5–7). Electronic FHR monitoring is an integral facet of modern obstetrics (8). Many obstetricians believe that diminished FHR variability most reliably predicts fetal distress (9). Normal FHR variability is considered reassuring (10), and decreased or absent variability is often associated with fetal acidosis and low Apgar scores (11). However, diminished variability is not specific for fetal acidosis/hypoxia. Other causes include fetal sleep cycles and maternal analgesic administration (9). These reductions in FHR variability may deprive obstetricians of a valuable monitor of fetal well-being. We therefore analyzed FHR tracings after epidural fentanyl supplementation of epidural lidocaine analgesia.

Methods and Materials

The Clinical Research Practices Committee approved this protocol, and we obtained written informed consent from all study participants. Patients in established, painful labor requesting epidural analgesia were candidates for study. Exclusion criteria included premature labor, previous cesarean section, cervical dilatation >7 cm, toxemia, diabetes, known fetal anomalies, thick meconium, and preepidural FHR evidence of fetal distress. Fetal heart rate was monitored with an internal fetal scalp electrode placed at least 15 min before the epidural catheter insertion. Uterine displacement was assured throughout the study period.

We inserted lumbar epidural catheters and sequentially tested for intrathecal and intravenous placement with 2% lidocaine, 2 and 5 mL, respectively. If necessary, an additional 5 mL of 1.5% lidocaine was injected to obtain satisfactory labor analgesia. At least 15 min after the last epidural lidocaine injection, we randomly administered epidurally either 75 μg fentanyl or saline in a 5-mL volume.

Received from the Departments of Anesthesia and Obstetrics, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina. Accepted for publication August 6, 1990.

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Fetal heart rate tracings were examined in 14 observation periods: 15 min before epidural placement (baseline), 15 min after establishment of adequate epidural lidocaine analgesia, and at 5-min intervals for 1 h after epidural fentanyl or placebo injection. Both the patient and the perinatologist interpreting the tracing were blinded to the study solution.

Fetal heart rate parameter analysis included baseline rate, presence of decelerations (variable or late), presence of accelerations, and long-term variability (10). We used our standardized institutional FHR variability scoring system: 0, ≤5 beats/min variability; 1, 6–10 beats/min variability; and 2, >10 beats/min variability. This is a modification of our earlier FHR variability scoring system that categorized variability into greater than or less than 10 beats/min (12).

We recorded maternal age, height, weight, gravidity, parity, and cervical dilation at time of epidural placement; neonatal Apgar scores; the frequency of maternal respiratory rates less than 12 or neonatal respiratory depression (1- or 5-min Apgar respiratory score = 0 or 1); and maternal hypotension (>20% systolic blood pressure reduction).

Statistical analysis of demographic variables included χ^2 Wilcoxon rank-sum tests, Student's *t*-tests, and analysis of variance, as appropriate. Univariate repeated-measures analysis of variance assessed treatment group and time effects on absolute FHR. Because the variability, accelerations, and deceleration scores were either categorical or ordinal, we performed several statistical analysis. χ^2-Tests were performed at each time period to assess differences between groups in FHR decelerations, accelerations, and variability scores (noncontinuous variables). To futher increase analysis sensitivity, we also grouped the low and intermediate variability scores and compared them with the high variability scores and repeated the analysis of variance with repeated measures. Finally, assuming that FHR acceleration, deceleration, and variability scores were at least ordinal, we performed repeated-measures analysis of variance on the ranks of the data. A *P* value <0.05 was considered to be statistically significant.

Results

We studied 40 parturients ($n = 20$ for epidural fentanyl and $n = 20$ for saline-placebo). One patient in the fentanyl group delivered before completion of the study and was excluded from data analysis.

There was no difference in maternal or neonatal demographics (Table 1). Two neonates (both from the placebo group) had Apgar scores <7, one of whom was subsequently found to have congenital heart disease. Baseline FHRs were similar in both groups (Figure 1). The incidence of variable or late decelerations was also similar in both groups and did not change with time. Fentanyl administration did not influence either FHR variability or the presence of accelerations (Figures 2 and 3). Although none of the FHR parameters differed between groups, FHR variability and percent of tracings with accelerations diminished significantly over time, independent of fentanyl administration ($P < 0.003$).

Table 1. Demographic Characteristics

	Patient group	
	Fentanyl ($n = 19$)	Saline ($n = 20$)
Patient age (yr)	28 ± 1	26 ± 1
Height (cm)	164 ± 1	162 ± 1
Weight (kg)	83 ± 2	78 ± 4
Cervical dilatation (cm)	4.0 ± 0.3	3.8 ± 0.9
1-min Apgar <7	0/19	2/20
5-min Apgar <7	0/19	1/19
Hypotension[a]	4/19	4/20
Receiving pitocin	8/19	8/20

Values for age, height, weight, and cervical dilatation are expressed as mean ± SEM.

[a] Greater than 20% reduction in systolic blood pressure.

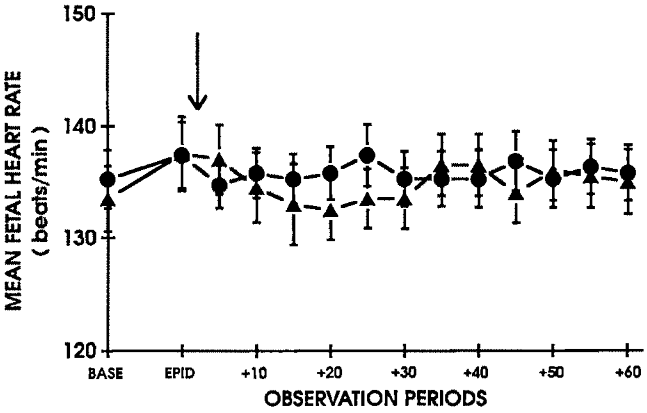

Figure 1. Mean (± SEM) fetal heart rate. BASE, 15 min average FHR before injection of epidural lidocaine; EPID, 15 min average FHR during epidural lidocaine analgesia before injection of epidural fentanyl or saline; arrow, injection of 75 μg fentanyl or saline; +10, average FHR at 10-min intervals, after epidural fentanyl/saline injection.

Discussion

One consequence of utilizing narcotics during labor is the possibility of diminishing the effectiveness of

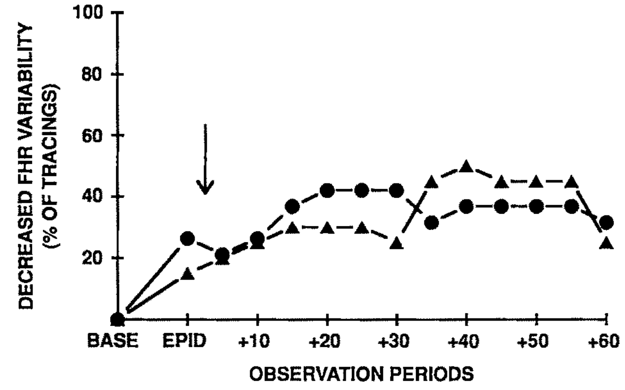

Figure 2. Percent of fetal heart rate tracings with decrease in variability below baseline levels. BASE, 15 min baseline observation period, before epidural lidocaine; EPID, 15 min average during epidural lidocaine analgesia before epidural fentanyl or saline; arrow, injection of 75 μg fentanyl or saline; +10, FHR variability at 10-min intervals after epidural fentanyl/saline injection.

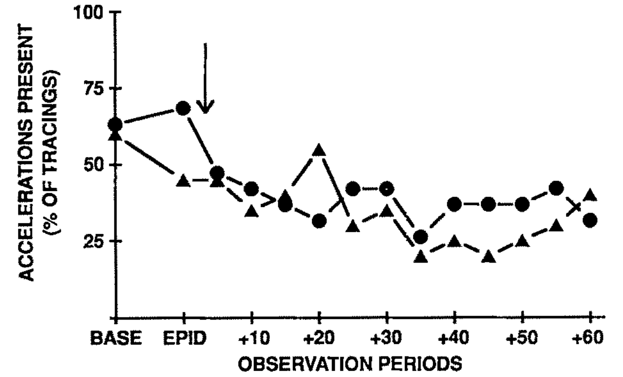

Figure 3. Percent of fetal heart rate tracings showing accelerations. BASE, 15 min baseline observation period before epidural placement; EPID, during epidural lidocaine analgesia; arrow, injection of 75 μg fentanyl or saline; +10, FHR accelerations above baseline at 10-min intervals after epidural fentanyl/saline injection.

FHR monitoring. The lack of changes in FHR in our study after epidural fentanyl is in contrast to reports of reductions in FHR variability after systemic administration of meperidine, morphine, or fentanyl (5–7).

Several investigators have reported diminished short-term FHR variability after intravenous meperidine or morphine when computer-aided short-term FHR variability (beat-to-beat) was analyzed (5,6). Computer analysis of the fetal R-R interval may be more sensitive in identifying subtle variability changes. However, clinical assessment of FHR variability is based primarily on long-term variability. Changes in short- and long-term variability usually occur in parallel (10). Our aim was to mimic the common clinical situation, where visual interpretation of long-term FHR variability is usually employed (10).

Recently, Rayburn et al. (7) studied long-term FHR variability changes in 49 laboring women given 50–100 μg/h intravenous fentanyl. In 49% of parturients, long-term variability decreased after fentanyl administration. These intravenous doses could transiently produce maternal fentanyl plasma levels far in excess of the expected minimal fentanyl plasma levels that would follow our single epidural administration of 75 μg fentanyl (13). The resulting fetal plasma levels might be high enough to produce FHR variability changes.

The above studies (5–7) of intravenous narcotics suffer from flaws in experimental design. All, for example, utilize FHR recordings before narcotic administration as the only control or baseline data, and none were blinded, randomized, or placebo-controlled.

The lack of effect on FHR associated with epidural fentanyl in our study probably reflects the relative low dose of fentanyl administered and the maternal and fetal pharmacokinetics of epidural fentanyl. Although low plasma fentanyl levels are generally reported after a single administration of epidural fentanyl, systemic absorption of epidural fentanyl may be highly variable, especially when using radioimmunoassay techniques (14). For example, in a study of nonpregnant patients three of eight patients had no detectable plasma fentanyl concentrations after epidural fentanyl; the remaining patients had maximum plasma fentanyl levels of 0.4–4.1 ng/mL (15). Other investigators using radioimmunoassay techniques report that 80 μg epidural fentanyl attains peak maternal plasma levels of 0.5–1.0 ng/mL within 5–20 min after epidural administration in laboring women (2,13,16,17). Similarly, when utilizing gas-liquid chromatographic assay of blood, fentanyl could be detected in the plasma in only two of six nonpregnant patients after 1 μg/kg epidural fentanyl. The preponderance of the literature reports very low maternal fentanyl plasma/blood levels after a single administration of epidural fentanyl.

The fetal effects that follow bolus epidural fentanyl are minimal. In pregnant sheep, fentanyl's maternal/fetal arterial plasma ratio stabilizes at approximately 2.5 between 20 and 60 min after bolus epidural fentanyl administration (18). This ratio would further reduce fetal exposure to epidural and minimize fetal effects. In addition, FHR, blood pressure, arterial pH, and uterine blood flow do not change significantly in pregnant sheep after 50–100 μg epidural fentanyl (19). We administered epidural fentanyl in dosages similar to these reports and found no changes in FHR. Because we observed the FHR for 60 min after epidural fentanyl injection, it is likely that any fetal effects of fentanyl would have been noted.

Our finding of significant changes over time in

FHR variability and percent of fetuses with FHR accelerations deserves further commentary. Although there were no differences between fentanyl and saline-treated groups, both groups showed significant changes from baseline levels during the period of observation. The reductions in FHR variability and accelerations may be associated with epidurally administered lidocaine or some other factor associated with labor.

The association of epidurally administered lidocaine during labor with diminished FHR variability or accelerations is controversial. Boehm et al. (20) studied changes in short- and long-term FHR variability after maternal epidural lidocaine injection with and without epinephrine. Patients with significant reductions in blood pressure (defined as <100 torr) were excluded. One of four patients receiving plain lidocaine developed "minimal" reductions in FHR variability within 5 min of epidural injection that persisted for 9 min. In the same study, 7 of 11 patients receiving lidocaine with 1:200,000 epinephrine also developed reduced FHR variability of similar onset and duration. Hehre and coworkers (21) examined short-term variability in 18 laboring women receiving epidural analgesia. Seven milliliters of 2% lidocaine with epinephrine 1:200,000 was utilized. These authors reported decreased variability "in the majority" of patients, beginning 6 min after injection and persisting for 4 min. No statistical methods were mentioned, and maternal blood pressure was not reported. Other investigators report no significant FHR variability reductions after epidural lidocaine labor analgesia (with and without epinephrine) (22,23). These were unblinded studies, and FHR accelerations were not analyzed.

We did not add epinephrine to our epidural lidocaine and thus avoided the possible confounding effects of epinephrine on the fetus or on uterine blood flow. Still, we discovered small but clinically recognizable reductions in FHR variability and accelerations. If there are FHR variability changes that follow epidural fentanyl, they are small and probably clinically insignificant. We estimate, using our observed group differences, that the number of patients needed to demonstrate a 6% difference in FHR variability would be in excess of 500 (24).

A difficulty with our experimental design as well as with other similar studies is the absence of true control data obtained in patients given no analgesia. Ethical considerations, however, prohibit withholding labor analgesia from women who desire it. Thus, randomizing patients to receive an epidural or no analgesia is difficult if not impossible. Women who do not desire analgesics during labor may not be suitable controls for those who strongly desire such therapy. Most investigations have utilized a period of time before analgesic use as their control and made FHR comparisons to a later period of labor, after an analgesic intervention has been made, but such data are baseline data, not true controls. Unfortunately, labor is a dynamic process, with duration, frequency, and intensity of contractions all increasing throughout it (25). Thus, differentiating analgesic effect from the effect of advancing labor is difficult.

In summary, because epidural injections of fentanyl or saline in parturients given lidocaine epidural analgesia for labor were both associated with statistically significant but equal reductions in FHR variability and the frequency with which FHR accelerations occurred, we conclude that epidural fentanyl alone has no significant effect on FHR under the conditions of our study. The clinical significance of these moderate reductions in FHR parameters during epidural lidocaine analgesia is unclear.

References

1. Skerman JH, Thompson BA, Goldstein MI, Jacobs MA, Gupta A, Blass NH. Combined continuous epidural fentanyl and bupivacaine in labor: a randomized study. Anesthesiology 1985;63:A450.
2. Vella LM, Willatts DG, Knott C, Lintin DJ, Justins DM, Reynolds F. Epidural fentanyl in labour. Anaesthesia 1985;40:741–7.
3. Justins DM, Francis D, Houlton PG, Reynolds F. A controlled trial of extradural fentanyl in labour. Br J Anaesth 1982;54:409–14.
4. Chestnut DH, Owen CL, Bates JN, Ostman LG, Choi WW, Geiger MW. Continuous infusion epidural analgesia during labor: a randomized, double-blind comparison of 0.0625% bupivacaine/0.0002% fentanyl versus 0.125% bupivacaine. Anesthesiology 1988;68:745–59.
5. Petrie RH, Yeh S, Murata Y, et al. The effect of drugs on fetal heart rate variability. Am J Obstet Gynecol 1978;130:294–9.
6. Zimmer EZ, Divon MY, Vadasz A. Influence of meperidine on fetal movements and heart rate beat-to-beat variability in the active phase of labor. Am J Perinatol 1988;5:197–200.
7. Rayburn WF, Smith CV, Parriott JE, Woods RE. Randomized comparison of meperidine and fentanyl during labor. Obstet Gynecol 1989;74:604–6.
8. Repke JT, Ferguson JE II. Fetal monitoring and fetal distress. In: Albright GA, Ferguson JE II, Joyce TH III, Stevenson DK, eds. Anesthesia in obstetrics. Boston: Butterworth Publishers, 1986:551–66.
9. Freeman RK, Garite TJ. Basic pattern recognition. In: Freeman RK, Garite TJ, eds. Fetal heart rate monitoring. Baltimore: Williams & Wilkins, 1981:63–83.
10. Parer JT. Fetal heart rate. In: Creasy RK, Resnik R, eds. Maternal-fetal medicine: principles and practice. Philadelphia: WB Saunders, 1989:314–43.
11. Paul RH, Suidan AK, Yeh S, Schifrin BS, Hon EH. Clinical fetal monitoring. VII. The evaluation and significance of intrapartum baseline FHR variability. Am J Obstet Gynecol 1975;123:206–10.

12. Meis PJ, Hobel CJ, Ureda JR. Late meconium passage in labor—a sign of fetal distress? Obstet Gynecol 1982;59:332–5.
13. Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA, Cousins MJ. Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. Pain 1989;38:253–9.
14. Wolfe JJ, Davies GK. Analgesic action of extra-dural fentanyl. Br J Anaesth 1980;52:357–8.
15. Justins DM, Knott C, Luthman J, Reynolds F. Epidural versus intramuscular fentanyl. Anaesthesia 1983;38:937–42.
16. Lampl E, Garen D, Levron P, Pathier D, Cousin MT. Pharmacokinetics of fentanyl given by the epidural route in women in labour. J Gynecol Obstet Biol Reprod 1986;15:603–7.
17. Schuttler J, White PF. Optimization of the radioimmunoassays for measuring fentanyl and alfentanil in human serum. Anesthesiology 1984;61:315–20.
18. Craft JB Jr, Coaldrake LA, Bolan JC, et al. Placental passage and uterine effects of fentanyl. Anesth Analg 1983;62:894–8.
19. Craft JB Jr, Robichaux AG, Kim H-S, et al. The maternal and fetal cardiovascular effects of epidural fentanyl in the sheep model. Am J Obstet Gynecol 1984;148:1098–104.
20. Boehm FH, Woodruff LF, Growdon JH. The effect of lumbar epidural anesthesia on fetal heart rate baseline variability. Anesth Analg 1975;54:779–82.
21. Hehre FW, Hood R, Hon EH. Continuous lumbar peridural anesthesia in obstetrics. VI: The fetal effects of transplacental passage of local anesthetic agents. Anesth Analg 1969;48:909–13.
22. Abboud TK, Khoo SS, Miller F, Doan T, Henriksen EH. Maternal, fetal, and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine. Anesth Analg 1982;61:638–44.
23. Abboud TK, David S, Nagappala S, et al. Maternal, fetal, and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. Anesth Analg 1984;63:973–9.
24. Sokal RR, Rohlf FJ. Biometry. 2nd ed. New York: WW Freeman and Company, 1981:263.
25. Fishburn JI, Greiss FC, Hopkinson R, Rhyne AL. Response of the gravid uterine vasculature to arterial levels of local anesthetic agents. Am J Obstet Gynecol 1979;133:753–7.

Tracheal Insufflation of Oxygen at Low Flow: Capabilities and Limitations

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MACKENZIE CF, BARNAS G, NESBITT S. Tracheal insufflation of oxygen at low flow: capabilities and limitations. Anesth Analg 1990;71:684–90.

Tracheal insufflation of oxygen (TRIO) may provide temporary oxygenation for patients or sustain life in apneic mass casualties when conventional ventilatory techniques are not available or feasible. Logistically, minimum flows of TRIO ($\dot{V}_{min}$) are desirable for field use and to reduce barotrauma should airway obstruction occur. We carried out a feasibility study to determine the efficacy of $\dot{V}_{min}$ of TRIO delivered within 1 cm of the carina, in nine anesthetized and paralyzed dogs. Minimum flows of TRIO for these dogs of average weight (12 kg) was 91 mL/min. In six of the dogs $\dot{V}_{min}$ TRIO was continued and provided oxygenation for an average of 1.5 h compatible with subsequent resuscitation with conventional ventilation. However, $Paco_2$ levels increased to mean values of 256 mm Hg in the 90 min. To determine what the effect of increased gas mixing was on gas exchange, we repeated $\dot{V}_{min}$ TRIO for 10 min in six of the dogs with and without high frequency oscillations superimposed on the TRIO flow. The oscillations (60 mL at 16.3 Hz) increased carbon dioxide excretion but significantly impaired oxygenation. In completely apneic animals, TRIO at low flow delivered by cricothyroidotomy may be useful as an emergency procedure when upper airway obstruction limits the use of other airway management techniques. However, enhancement of gas mixing during low-flow TRIO impairs oxygenation, so that higher flows would be required when respiratory efforts occur.

Key Words: VENTILATION, TRACHEAL INSUFFLATION.

Tracheal insufflation of oxygen (TRIO) is a technique of continuous flow ventilation, similar to apneic oxygenation, that can sustain life in apneic anesthetized dogs for up to 5 h (1). The major clinical advantages of TRIO over apneic oxygenation are that TRIO does not require denitrogenation with 100% oxygen (O_2) for efficacy. Tracheal insufflation of O_2 delivered within 1 cm of the carina also results in carbon dioxide (CO_2) excretion proportional to O_2 flow (1). With apneic oxygenation, no CO_2 is removed (2–4) because there is only a unidirectional movement of O_2 into the alveoli. The historical literature on TRIO has been previously summarized (1,5). Recent studies indicate that the mechanisms of gas exchange include cardiogenic oscillations, molecular diffusion, and convection close to the exit of O_2 at the carina (6,7). Carbon dioxide excretion was greatly improved in partially paralyzed spontaneously breathing dogs when TRIO of 5 L/min was applied (8). Tracheal insufflation of O_2 is advocated for mass casualties (5) and as a temporary measure in nonideal circumstances when tracheal intubation cannot be instituted (1).

Tracheal insufflation of O_2 delivered by a catheter placed through a cricothyroidotomy cannula could be useful in field and emergency circumstances in which technical difficulty, upper airway obstruction, or lack of equipment make conventional tracheal intubation and ventilation not feasible (5). Prolonged (>1 h) use of TRIO from a limited O_2 supply would require minimum flows of O_2 compatible with adequate oxygenation. In addition, minimum flows would be advantageous to reduce barotrauma during the in-hospital or field use of TRIO and in the presence of upper airway obstruction. If sufficiently low flows are used, continuous exhalation may occur through the space between the TRIO catheter and the cricothyroidotomy cannula even when complete upper air-

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Supported by U.S. Army Medical Research and Development Command under Contract No. DAMD 17-88-C8136.

Opinions, interpretations, conclusions and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army.

Received from the Anesthesiology Research Laboratories, Department of Anesthesiology, University of Maryland Medical System and School of Medicine, Baltimore, Maryland. Accepted for publication August 7, 1990.

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way obstruction is present. To establish the feasibility of low-flow TRIO we determined the minimum flow of TRIO ($\dot{V}_{min}$) compatible with Pa_{O_2} greater than 50 mm Hg after 30 min, and examined the cardiorespiratory function of animals ventilated at $\dot{V}_{min}$. To determine how gas exchange might be affected when gas mixing was increased in the airways, such as may occur in the field with suctioning, attempts at spontaneous respiration, or external chest compression, we superimposed high-frequency oscillations onto $\dot{V}_{min}$ TRIO.

Methods and Materials

In conducting this research we adhered to the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, revised 1985).

Nine dogs ranging in weight from 8 to 20 kg (mean ± SE, 12 ± 1 kg) were anesthetized with intravenous 30 mg/kg pentobarbital and tracheally intubated with a 1.5-mm internal diameter TRIO catheter outside an 9-mm internal diameter cuffed tracheal tube, the latter with two sampling lumina (Hi-Lo Jet, Mallinckrodt, Glens Falls, N.Y.). Anesthesia and neuromuscular paralysis were maintained with a continuous infusion of 3 $mg \cdot kg^{-1} \cdot h^{-1}$ thiamylal and 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium. Conventional mechanical ventilation (CMV) with room air began at a rate of 12 breaths/min and with a tidal volume sufficient to maintain Pa_{CO_2} at 35 ± 1.1 mm Hg. Pulmonary arterial and femoral arterial catheters were inserted. A pulse oximeter (Nellcor, Hayward, Calif.) was placed on the tongue for the continuous monitoring of arterial O_2 saturation (Sa_{O_2}). To ensure ideal gas exchange in this feasibility study, the tip of the TRIO catheter was adjusted using a fiberoptic bronchoscope so that it was 1 cm proximal to the carina.

Systemic arterial pressure (Part), pulmonary artery pressure (Ppa), airway pressure (Paw; monitored through a lumen in the wall of the Hi-Lo tracheal tube), and esophageal pressure (Pes; from a balloon placed in the lower third of the esophagus) were monitored by pressure transducers (Statham, Oxnard, Calif.). Electrocardiogram, Part, Ppa, Paw, Pes, and Sa_{O_2} were recorded continuously on an eight-channel ink-jet recorder (Mingograf Siemens, Elema, Sweden). A mass spectrometer (Med Spec II, Allegheny International, St. Louis, Mo.) calibrated with room air and factory calibrated 5.1% CO_2, 30.7% O_2, and 0% N_2 was used to simultaneously analyze airway O_2, N_2, and CO_2 during the experiments involving high-frequency superimposed oscillations (see below). No airway gas sampling was used during $\dot{V}_{min}$ determination. Full sets of measurements were made serially throughout the experiments and included arterial and mixed venous blood gas tensions and pH (sampled simultaneously and analyzed with temperature correction on IL713 Blood gas analyzer, Lexington, Mass.) and cardiac output ($\dot{Q}t$; measured by thermodilution using cardiac output computer 9520A American Edwards, Santa Ana, Calif.). Hemoglobin and arterial and mixed venous saturation were also measured from blood samples with a hemoximeter (OSM2 Radiometer, Copenhagen, Denmark).

First, adequacy of oxygenation at low-flow TRIO was established in each animal. Conventional mechanical ventilation was stopped and TRIO begun at flows of 100 mL/min O_2 delivered from the calibrated flow meter of an anesthesia machine (Forreger, New York, N.Y.). Whenever Sa_{O_2}, monitored by pulse oximeter, remained above 90% for 10 min and arterial blood gas analysis showed a Pa_{O_2} above 50 mm Hg, TRIO was stopped. The animal was then ventilated to achieve baseline Pa_{CO_2} by CMV. Progressively lower or higher flows of TRIO at increments of 10 mL/min were used for 10 min until the TRIO O_2 flow was determined at which the pulse oximeter Sa_{O_2} would decrease below 90% and Pa_{O_2}, when analyzed, would be near 50 mm Hg. The animal was ventilated back to baseline Pa_{CO_2} and 30 min of TRIO begun with O_2 flows 10 mL/min higher than those that produced Sa_{O_2} less than 90%. Measurements and blood samples were taken and recorded every 10 min. At the end of 30 min, provided Pa_{O_2} was greater than 50 mm Hg, this flow was defined as $\dot{V}_{min}$. The animal was then ventilated with CMV to restore baseline values of Pa_{CO_2}. In six of the dogs the duration of ventilation at $\dot{V}_{min}$ was established by continuing TRIO after 30 min. Full sets of measurements were made every 15 min for a further 30 min and then every 30 min thereafter. Tracheal insufflation of O_2 was stopped when a precipitous decrease in Part or Sa_{O_2} was observed; CMV was then reinstituted for 30–60 min before the dog was terminated.

In six of the dogs, we also determined the effects of increasing gas mixing by superimposing high-frequency oscillations (HFSO) on TRIO at $\dot{V}_{min}$. A triple-lumen catheter (7.5F) was positioned using fiberoptic bronchoscopy so that the three lumina were in a subsegmental bronchus (site 1), segmental bronchus (site 2), and mainstem bronchus (site 3). One lumen at the tip of the Hi-Lo jet tracheal tube

Table 1. Characteristics and Some Variables Studied in the Nine Dogs

Dog No.	Wt (kg)	$\dot{V}_{min}$ (mL O_2/min)	Rate of increase of $Paco_2$ during 30-min $\dot{V}_{min}$ TRIO (mm Hg $Paco_2$/min)	Duration of $\dot{V}_{min}$ TRIO (min)	Minimum Pao_2 mm Hg during $\dot{V}_{min}$ TRIO (mm Hg)	$\dot{V}_{min}$ TRIO ± HFSO
1	12	100	9.8	30	64	No
2	12	100	3.9	60	61	Yes
3	12	80	3.2	140	75	Yes
4	10	80	3.7	130	125	Yes
5	10	80	3.3	30	99	Yes
6	20	125	3.6	45	52	Yes
7	13	100	4.2	30	58	Yes
8	8	80	5.7	90	111	No
9	9	80	4.5	120	147	No
Mean ± SE	12 ± 1	91 ± 5	4.7 ± 0.7	97.5[a]	88 ± 11	

$\dot{V}_{min}$, minimum flow of tracheal insufflation of oxygen (TRIO); $Paco_2$, arterial carbon dioxide pressure; Pao_2, arterial oxygen pressure; HFSO, high-frequency oscillations.

[a] In those animals given $\dot{V}_{min}$ TRIO for more than 30 min.

Table 2. Mean ± SE of Cardiorespiratory Variables in Nine Dogs Given $\dot{V}_{min}$ TRIO for 30 min

Variable	Time of measurement			
	Baseline	10 min	20 min	30 min
HR (beats/min)	171 ± 9.2	129 ± 11.7	140 ± 12.9	143 ± 12.4
Part (mm Hg)	137 ± 6.4	128 ± 6.7	143 ± 6.6	148 ± 6.9
Ppa (mm Hg)	17 ± 0.7	23 ± 1.5[a]	26 ± 1.0[a]	28 ± 1.9[a]
Pao_2 (mm Hg)	103 ± 2.1	94 ± 8.3	96 ± 9.6	89 ± 9.1
$P\bar{v}o_2$ (mm Hg)	50 ± 1.3	63 ± 3.5	70 ± 4.5	68 ± 5.2
pHa	7.3 ± 0.01	7.0 ± 0.01[a]	6.9 ± 0.01[a,b]	6.8 ± 0.01[a,b,c]
$pH\bar{v}$	7.3 ± 0.01	7.0 ± 0.01[a]	6.9 ± 0.01[a,b]	6.9 ± 0.01[a,b,c]
$Paco_2$ (mm Hg)	35 ± 1.1	104 ± 7.9[a]	140 ± 13.6[a]	172 ± 20.8[a,b]
$P\bar{v}co_2$ (mm Hg)	40 ± 1.6	94 ± 7.5[a,d]	128 ± 10.8[a,d]	153 ± 15.1[a,b,d]
CI ($L \cdot min^{-1} \cdot m^2$)	3.5 ± 0.2	4.4 ± 0.4	4.6 ± 0.3[a]	4.6 ± 0.4
$\dot{V}o_2$ (mL/min)	71 ± 2.9	75 ± 3.4	70 ± 2.2	67 ± 1.8

HR, heart rate; Part, systemic arterial pressure; Ppa, pulmonary artery pressure; Pao_2, arterial O_2 tension; $P\bar{v}o_2$, venous O_2 tension; pHa, arterial pH; $pH\bar{v}$, venous pH; $Paco_2$, arterial CO_2 tension; $P\bar{v}co_2$, venous CO_2 tension; CI, cardiac index; $\dot{V}o_2$, O_2 consumption.

[a] $P < 0.05$, compared with baseline.

[b] $P < 0.05$, compared with 10-min data.

[c] $P < 0.05$, compared with 20-min data.

[d] $P < 0.05$, compared with arterial value at the same time.

sampled gas 5 cm above the carina (site 4). A piston pump driven by a linear motor was used to superimpose oscillations (60 mL at 16.3Hz) onto $\dot{V}_{min}$ TRIO. This technique differed from high-frequency jet ventilation and high-frequency oscillation in that the mean fresh gas flow was equal to $\dot{V}_{min}$. Arterial and mixed venous blood gases and airway gas samples from sites 1–4 were taken after 5 and 10 min of TRIO at $\dot{V}_{min}$. Baseline $Paco_2$ was then reestablished with CMV, and the measurements were repeated with HFSO. Mass spectrometer sampling time at each of the airway sites was 10 s with 10-s intervals between sampling sites 1–4. Statistical analysis used the paired and unpaired *t*-test with Bonferroni correction. $P <$ 0.05 was considered as significant.

Results

The minimum flow for 30-min TRIO was established as 91 ± 5 mL/min (mean ± SE) and was roughly correlated with body weight (Table 1). The larger animals generally required higher $\dot{V}_{min}$. Oxygen consumption ($\dot{V}o_2$) of about 70 mL/min, calculated as the product of the arteriovenous O_2 content difference and $\dot{Q}t$, was unchanged during $\dot{V}_{min}$ TRIO. Table 2 gives cardiorespiratory and $\dot{V}o_2$ values for the nine animals given TRIO for 30 min. Arterial O_2 tension was unchanged from baseline values measured on room air CMV, but Ppa increased and there was pronounced CO_2 retention and progressive respiratory acidosis. Cardiac index increased compared to

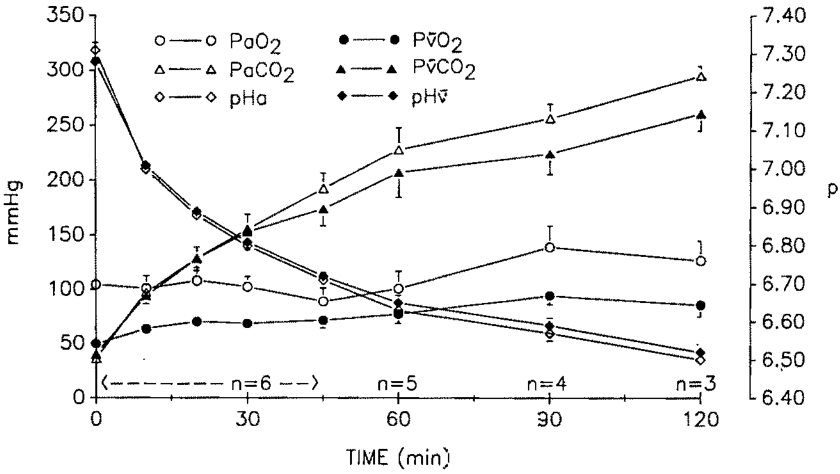

Figure 1. Mean ± SE of Po_2, Pco_2, and pH during prolonged minimum-flow TRIO of 91 ± 5 mL/min.

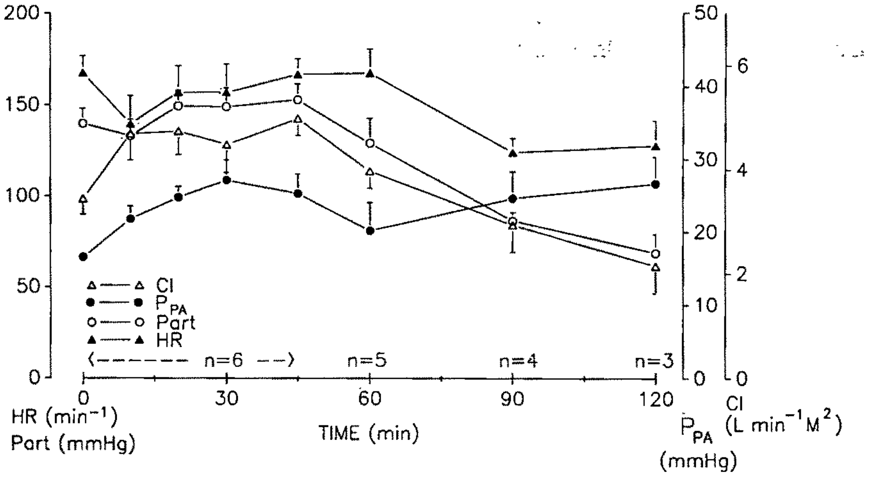

Figure 2. Mean ± SE of cardiorespiratory variables during prolonged minimum-flow TRIO of 91 ± 5 mL/min. *n* = number of dogs in displayed data.

baseline values during the 30-min $\dot{V}_{min}$ TRIO. The average duration of $\dot{V}_{min}$ TRIO in the six dogs where it was extended beyond 30 min was 97 min with a range of 45–140 min. Airway pressure was 0 cm H_2O, and Pes remained constant between 0 and −3 cm H_2O throughout TRIO, verifying the lack of respiratory efforts. Blood gas tensions, intravascular pressures, cardiac index, and heart rate are plotted in Figures 1 and 2 for these six dogs. In three dogs at 90, 130, and 140 min, respectively, systolic Part decreased below 80 mm Hg and the study was stopped. In three other animals $\dot{V}_{min}$ TRIO was stopped at 60 and 120 min with Part, Ppa, and $\dot{Q}t$ essentially unchanged from baseline, although Pao_2 progressively decreased (Figure 1).

In four of the six animals given $\dot{V}_{min}$ TRIO for more than 30 min, a return to room air CMV for 30–60 min restored baseline blood pressures and arterial CO_2, and returned pH and $\dot{Q}t$ to near baseline values. In one other animal after 130 min $\dot{V}_{min}$ TRIO, systolic Part decreased to 35 mm Hg on institution of CMV and the hypotension was reversed with 50 MEq $NaHCO_3$. In the sixth animal after 90-min $\dot{V}_{min}$ TRIO, systolic Part was restored by CMV but $\dot{Q}t$ remained low at 0.8 L/min compared to a baseline value of 1.8 L/min. No supplementary O_2 was given during CMV, and no inotropic support was used in any of the animals in this study.

Addition of HFSO to TRIO decreased O_2 (Table 3) and lowered ($P < 0.05$) the concentrations of O_2 at all four sampling sites after 5 min (Figure 3). At sites 1–4 there were increases in N_2 concentration ($P < 0.05$) at 5 min with the addition of HFSO. Arterial and airway CO_2 at sites 1–3 decreased ($P < 0.05$) with HFSO at both time points (Table 3 and Figure 3). The 10-min data with addition of HFSO were similar to the 5-min data. During TRIO without HFSO, O_2 concentration at 5 min was greater at sites 2 and 3 than at site 4. This difference was lost with addition of HFSO. Similarly, the differences in CO_2 concentrations among the various sites present during TRIO were disrupted by addition of HFSO at both time points. Oxygen and

Table 3. Arterial Blood Oxygen (Pa_{O_2}) and Carbon Dioxide (Pa_{CO_2}) After 5 and 10 min of TRIO or TRIO + HFSO in Six Dogs

	5 min		10 min	
	TRIO	TRIO + HFSO	TRIO	TRIO + HFSO
Pa_{O_2} (mm Hg)	75 ± 5.2	39 ± 3.0[a]	77 ± 6.9	35 ± 3.8[a]
Pa_{CO_2} (mm Hg)	80 ± 5.2	63 ± 3.0[a]	101 ± 6.0[b]	74 ± 4.8[a,b]

TRIO, tracheal insufflation of oxygen; HFSO, high-frequency superimposed oscillation.
[a] $P < 0.01$ compared with TRIO value.
[b] $P < 0.005$ compared with 5-min value.

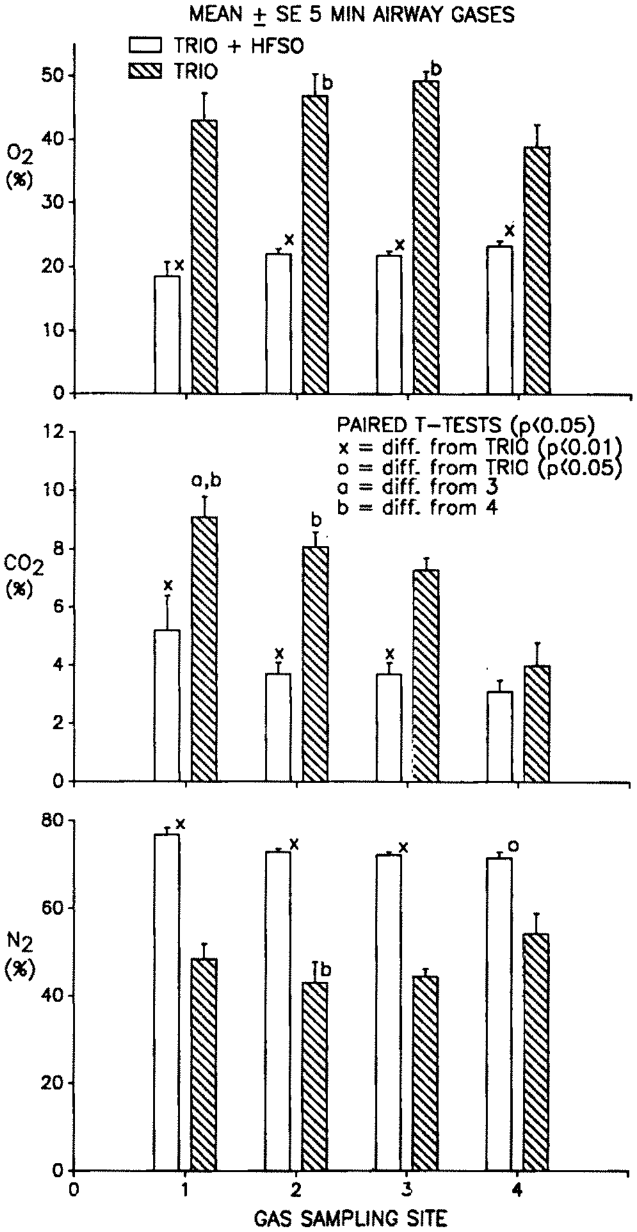

Figure 3. O_2, CO_2, and N_2 concentrations (%) simultaneously sampled from sites 1–4 (see text) with TRIO and TRIO + HFSO.

CO_2 removed from the airways with use of HFSO were replaced with N_2 found in similar quantities at each airway sampling site.

Discussion

Tracheal insufflation of O_2 at $\dot{V}_{min}$ is a physiological model of respiration where oxygenation is adequate but CO_2 excretion is extremely limited. In the first 10 min of $\dot{V}_{min}$ TRIO, Pa_{CO_2} increased rapidly from about 40 to 100 mm Hg, and then increased further to about 170 mm Hg in the next 20 min. As in human studies where CO_2 tension increased to this level, dysrhythmias rarely occurred (4). Among the dysrhythmias that occurred within this study none produced hemodynamic changes or persisted and required interventions to correct. We observed that in all nine dogs, arterial CO_2 tensions were consistently higher than venous tensions in all measurements made after starting TRIO (Table 2). We attribute this to the Haldane effect: O_2-poor blood transiting the lung can release very little CO_2 during $\dot{V}_{min}$ TRIO, and arterial CO_2 content is near venous levels. Consequently, the reduction of CO_2 binding that occurs when the blood is oxygenated in the lungs results in a greater Pa_{CO_2} for a given CO_2 content.

However, our results show that as TRIO progressed significant CO_2 excretion occurred during $\dot{V}_{min}$ TRIO (Figure 1). Slutsky et al. (1) presented an equation for prediction of alveolar ventilation for a given rate of increase in CO_2 during TRIO. If we modify the equation to account for the lower body weight of our dogs, it predicts an alveolar ventilation of about 500 mL/min for the 2.4 mm Hg/min increase we observed in Pa_{CO_2} between 10 and 60 min of TRIO. That this prediction grossly overestimates the flow actually delivered (91 mL/min) indicates that other mechanisms of CO_2 excretion were probably working. One factor may be the increase in gas mixing due to cardiogenic oscillations, because these are especially important as a gas-mixing mechanism during conditions of extreme hypoventilation (6,7). Another factor may be the large increase (about sevenfold after 1 h) in the diffusion gradient for CO_2 from the alveoli to the mouth.

Oxygenation with TRIO occurs because a high concentration of O_2 is established in the peripheral airways, facilitated by fresh gas flow entry within 1 cm of the carina. In the course of determining $\dot{V}_{min}$ several factors were noted to reduce the efficacy of

TRIO. Arterial O_2 saturation decreased during TRIO if neuromuscular blockade with pancuronium was insufficient, and slight respiratory efforts were noted by monitoring Pes. The decrease in $Sa{O_2}$ was reversed when additional pancuronium was given. Continuous mass spectrometer sampling (190 mL/min) was avoided during prolonged $\dot{V}_{min}$ TRIO because it caused arterial O_2 desaturation. We postulate the same mechanism for these decreases in $Sa{O_2}$ during TRIO as for HFSO. All produce enhanced gas mixing. During HFSO, the O_2 supply oscillates and causes ambient gas, with a lower O_2 concentration from the upper airways, to dilute the O_2 gradient established between the carina and the alveoli. As a result, additional N_2 dilutes the O_2 concentration in the peripheral airways so that alveolar O_2 and ultimately $Pa{O_2}$ is lowered. The limitation to the duration of TRIO, when not caused by hypoxemia, appeared to be due to cardiovascular depression secondary to hypercarbia and acidosis (1).

Clinical Application of Results

The use of TRIO for ventilation of patients involved in mass casualties has been advocated (5). The advantages of TRIO over a self-inflating bag or other ventilatory techniques are that only very simple equipment is needed and one rescuer can rapidly service many subjects. A cricothyroidotomy could be performed, the TRIO catheter positioned through the cricothyroidotomy cannula, and gas supplies connected expeditiously. The simplicity of the technique would enable ventilation to be achieved in situations where there is limited access for other equipment. No further ventilatory interventions would be required while the gas supplies last. The results from the present study show that TRIO may be useful for mass casualties, and we have demonstrated that the O_2 supply required by a given casualty could be relatively small, especially for short ventilatory maintenance periods. The observation that extremely low O_2 flows may be compatible with survival is a very important factor to consider in emergency field situations, because O_2 supplies are likely to be limited. The lower the flow the longer will be the possible period of ventilatory support and survival from a given O_2 supply. Because we found that increased mixing decreases oxygenation during low-flow TRIO, we do not think low-flow TRIO would be efficacious in the field situation unless there was no attempt at spontaneous breathing. If spontaneous breathing occurred, higher TRIO flows than $\dot{V}_{min}$ would be required to prevent contamination of alveolar O_2 with air. This higher flow technique is reported to be beneficial (8).

In the present experiments, we tested $\dot{V}_{min}$ TRIO under optimal conditions: the dogs had healthy lungs and were paralyzed, and the TRIO catheter was placed through the larynx and its position checked with bronchoscopy. Before this prototype $\dot{V}_{min}$ TRIO technique could be considered for field and emergency use, however, several considerations need to be evaluated. The efficacy of gas exchange during $\dot{V}_{min}$ TRIO in animals with lung injuries and complications, such as pulmonary edema, secretions, partial airway obstruction, and ventilation-perfusion mismatch, or when the TRIO catheter is not precisely positioned, still needs to be determined. In addition, if considered for use in humans $\dot{V}_{min}$ would be greater because human O_2 consumption is higher and functional residual capacity and physiological dead space are greater than in anesthetized dogs.

The circumstances in which we believe $\dot{V}_{min}$ TRIO may be beneficial include inability to ventilate with a resuscitator bag and mask used with oral or nasopharyngeal airways combined with failure of conventional tracheal intubation. A TRIO catheter may then be passed either translaryngeally or through a cricothyroidotomy cannula. If partial laryngeal obstruction is present, passage of a 1.5-mm internal diameter catheter may be possible when conventional tracheal tube insertion is technically impossible. Our present results show that oxygenation may be delivered at low flows that would not cause excessive intrapulmonary pressures if airway resistance were particularly high or flow of expired gases were limited by secretions. This technique should therefore be included among the management strategies for failed intubation in the apneic patient with a previously unrecognized difficult or partially obstructed airway.

In conclusion, TRIO at very low flows of 91 ± 5 mL/min can sustain life in apneic dogs for more than 2 h without denitrogenation or preoxygenation. However, cardiovascular depression gradually occurs, apparently due to high $Pa{CO_2}$ and acidosis. The principle that oxygenation is impaired with increased gas mixing during TRIO at low flow limits the clinical usefulness of the low-flow TRIO technique to situations of complete apnea.

References

1. Slutsky AS, Watson J, Leith DE, et al. Tracheal insufflation of O_2 (TRIO) at low flow rates sustains life for several hours. Anesthesiology 1985;63:278–86.
2. Holmdahl MH. Pulmonary uptake of oxygen, acid-base metab-

olism, and circulation during prolonged apnoea. Acta Chir Scand 1956;212(Suppl):33–9.

3. Draper WB, Whitehead RW. Diffusion respiration in the dog anesthetized by pentothal sodium. Anesthesiology 1944;5:262–73.
4. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. Anesthesiology 1959;20:789–98.
5. Slutsky AS. Non conventional methods of ventilation. Am Rev Respir Dis 1988;138:175–83.
6. Burwen DR, Watson J, Brown R, et al. Effect of cardiogenic oscillations on gas mixing during tracheal insufflation of oxygen. J Appl Physiol 1986;60:965–71.
7. Miura S, Takahashi H, Shioya T, et al. Effect of cardiogenic gas mixing on alveolar arterial difference during hypoventilation. Am Rev Respir Dis 1988;137:270.
8. Long SE, Menon AS, Kato H, et al. Constant oxygen insufflation (COI) in a ventilatory failure model. Am Rev Respir Dis 1988; 138:630–5.

Emergency Tracheal Intubation in the Postanesthesia Care Unit: Physician Error or Patient Disease?

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MATHEW JP, ROSENBAUM SH, O'CONNOR T, BARASH PG. Emergency tracheal intubation in the postanesthesia care unit: physician error or patient disease? Anesth Analg 1990;71:691–7.

Inadequate airway maintenance has been a major factor in perioperative morbidity. To determine the incidence and etiology of emergency tracheal intubations in the postanesthesia care unit (PACU), we retrospectively reviewed 13,593 consecutive admissions to our PACU from October 1986 through October 1988. Twenty-six patients (26/13,593 = 0.19%) required the insertion of an endotracheal tube while in the PACU. Seventy-seven percent (20/26) of the intubations occurred within 1 h of extubation and/or admission to the PACU. Intubation was more common at the extremes of age; 54% of those intubated were more than 60 yr old ($P = 0.003$); 19% were less than 3 yr old ($P < 0.05$). Twenty-three percent of the intubated patients had undergone otolaryngologic procedures ($P = 0.008$). Interestingly, 73% of the intubations occurred during the months of January through June ($P = 0.016$). Median PACU admission scores were lower for the intubated group ($P < 0.001$). There was no association between intubation and gender ($P = 0.74$), anesthetic technique ($P = 0.41$), or anesthetic agent ($P = 0.49$). Of the 26 intubations, 18 (69%) were considered to be directly related to anesthetic management. Despite the extremely low incidence of emergency tracheal intubation in a heterogeneous group of patients admitted to our PACU, preventable anesthesia-related etiologic factors including excessive sedative or anesthetic effect, inappropriate fluid management, persistent muscle relaxant effect, and upper airway obstruction contributed to the majority of these intubations.

Key Words: COMPLICATIONS, POSTOPERATIVE—reintubation. INTUBATION, TRACHEAL—postoperative.

Inadequate airway maintenance has been a major factor in perioperative morbidity (1). Residual anesthetic effects and anatomic distortions secondary to surgery, as well as exacerbations of a patient's underlying illnesses, can all affect the management of a patient's airway in the postanesthesia care unit (PACU). Ventilatory impairment so severe as to require tracheal intubation is clearly a life-threatening complication (2). Therefore, we retrospectively reviewed the records of patients admitted to our PACU (n = 13,593 patients) over a period of 25 mo from October 1986 through October 1988 to determine the incidence and etiology of all the emergency intubations occurring in the immediate recovery period.

Methods

Subsequent to approval from the Human Investigation Committee of the Yale University School of Medicine, data from all patients admitted to our postanesthesia care unit from October 1986 through October 1988 that had been entered in a computerized database were analyzed (3). Patients from all surgical services except obstetrics, cardiac, ambulatory surgery, and ophthalmology were admitted to this PACU. Patients admitted directly to an intensive care unit were not included in the database. The data sheets used to compile the database consisted of two parts. The first listed premedications, if any, defined intraoperative complications, and was completed upon admission to the PACU by the anesthesiologist involved in the patient's intraoperative care. The

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Presented in part at the 1989 International Anesthesia Research Society meeting, Lake Buena Vista, Florida, March 1989.

Received from the Departments of Anesthesiology and Medicine, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication August 8, 1990.

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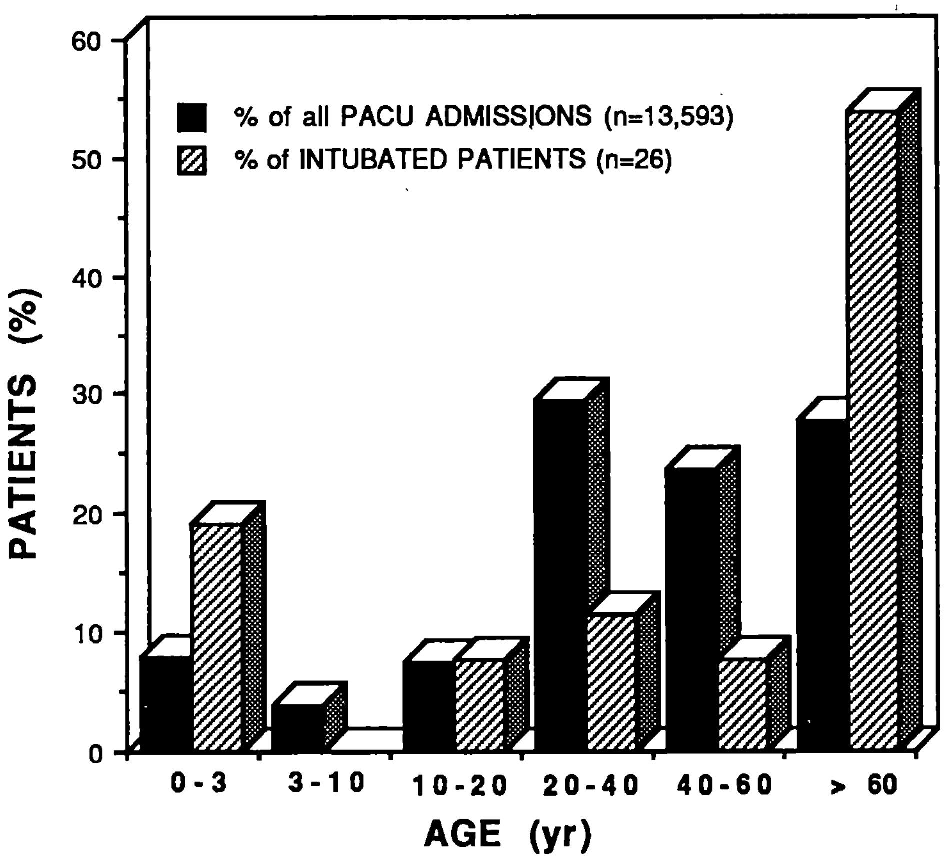

Figure 1. Age distribution of patients intubated in the PACU in comparison with the entire PACU population. The highest incidence of intubation while the patient was in the PACU was in the 0–3-yr and the more than 60-yr age groups.

second part was completed by the PACU nurses before discharge from the PACU and contained information on the patient's course in the PACU including admission scores—an evaluation based on color (3/9), consciousness (3/9), and respiration (3/9), and yielding a total possible score of 9. In addition, body temperature, hemodynamic stability, need for respiratory support, altered mental status, and medications administered were documented. Emergency intubation, in our study, was defined as the insertion of an endotracheal tube for airway support while the patient was in the PACU regardless of whether or not the patient had been intubated while in the operating room. For all patients identified as requiring endotracheal intubation in the PACU, the complete hospital chart and detailed anesthesia and recovery records were reviewed for information concerning the patient's preoperative, intraoperative, and postoperative course. We also reviewed the notes of physicians present at the time of intubation as well as incident reports that may have been filed but were not part of the formal hospital records. If multiple etiologic factors for intubation were present, these notes and incident reports were used to determine the predominant reason for intubation. Statistical analysis was performed using χ^2 (age > 60 yr, gender, anesthetic agent, time of year), Fisher's exact test (anesthetic technique, surgical service, age < 3 yr, ASA physical status classification), and the Wilcoxon rank-sum test (median PACU admission scores); $P < 0.05$ was considered to be significant.

Results

From October 1986 through October 1988 there were 13,593 consecutive admissions to the PACU. Airway support with an endotracheal tube, pharyngeal airway, nasal airway, manual jaw lift, or verbal support was necessary in 8.5% (1161/13,593) of patients. Twenty-six patients (26/13,593 = 0.19%) required the insertion of an endotracheal tube while in the PACU. Two patients (2/26) had received a regional (spinal, epidural) technique in the operating room that did not require endotracheal intubation. Clinical criteria including apnea, tachypnea, cyanosis, and increased work of breathing were used by the physicians in the PACU to evaluate the need for intubation. However, in 15 patients (15/26 = 58%), objective data in the form of inadequate arterial blood gasses or an oxygen saturation measurement of less than 90% on supplemental oxygen therapy were used to aid in the

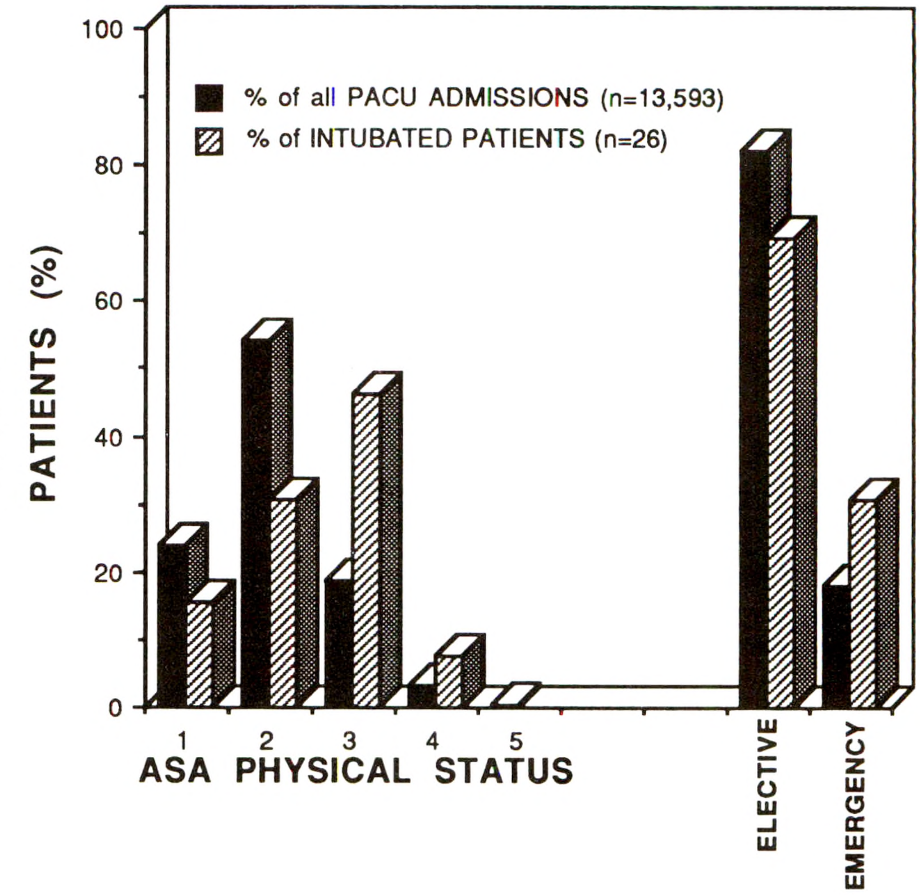

Figure 2. Distribution of patients intubated in the PACU according to ASA physical status in comparison to the entire PACU population. Forty-six percent of those intubated in the PACU had mild or no systemic disease (ASA physical status I and II); 54% had severe systemic disease (ASA physical status III and IV).

decision to intubate. The distribution of patients according to age, ASA physical status classification, length of surgery, and time to intubation while they were in the PACU are shown in Figures 1–4. Of the 26 intubations, 18 (69%) were considered by retrospective review to be directly related to anesthetic management (Table 1). The seven cases of intubation secondary to airway obstruction due to head and neck pathology were 0.7% (7/951) of the otolaryngologic patients admitted to the PACU in the period reviewed. Of these seven patients ($n = 7$), two bled at the operative site, three sustained postoperative laryngeal edema, one sustained airway obstruction secondary to a large goiter, and one had pulmonary edema after tonsillectomy for marked upper airway obstruction. Of the six patients with inappropriate fluid management, five presented with pulmonary edema. In contrast, the sixth patient had a primary circulatory arrest (hypovolemia) leading to a respiratory arrest in the setting of preoperative volume depletion, intraoperative blood loss, a spinal anesthetic-induced vasodilation, and inadequate fluid replacement. All six patients with excessive sedative or anesthetic effect demonstrated impaired ventilation upon admission to the PACU, with findings ranging from apnea resulting in treatment with naloxone (3/6) to elevated $\mathrm{PaCO_2}$ on arterial blood gas analysis (2/6). All three of the patients who had persistent muscle relaxant effects were initially treated in the PACU with additional anticholinesterase drugs. Of these three patients, one had an infiltrated intravenous catheter that probably resulted in delayed subcutaneous absorption of pancuronium; the other two had inadequate reversal demonstrated by a neuromuscular blockade monitor while in the PACU. Finally, one patient met no clear clinical or objective criteria for intubation and was considered to have probably been intubated unnecessarily due to hasty action on the part of the PACU team. There were no significant associations between intubation and gender ($P = 0.74$), anesthetic technique ($P = 0.41$), or anesthetic agent ($P = 0.49$). There was, however, an association between age and intubation ($P = 0.004$). Fifty-four percent (14/26) of the intubations occurred in patients more than 60 yr of age, whereas only 28% of those not intubated were older than 60 ($P = 0.003$). Similarly, 19% (5/26) of the intubations occurred in the 0–3-yr age group; only 8% of those not intubated

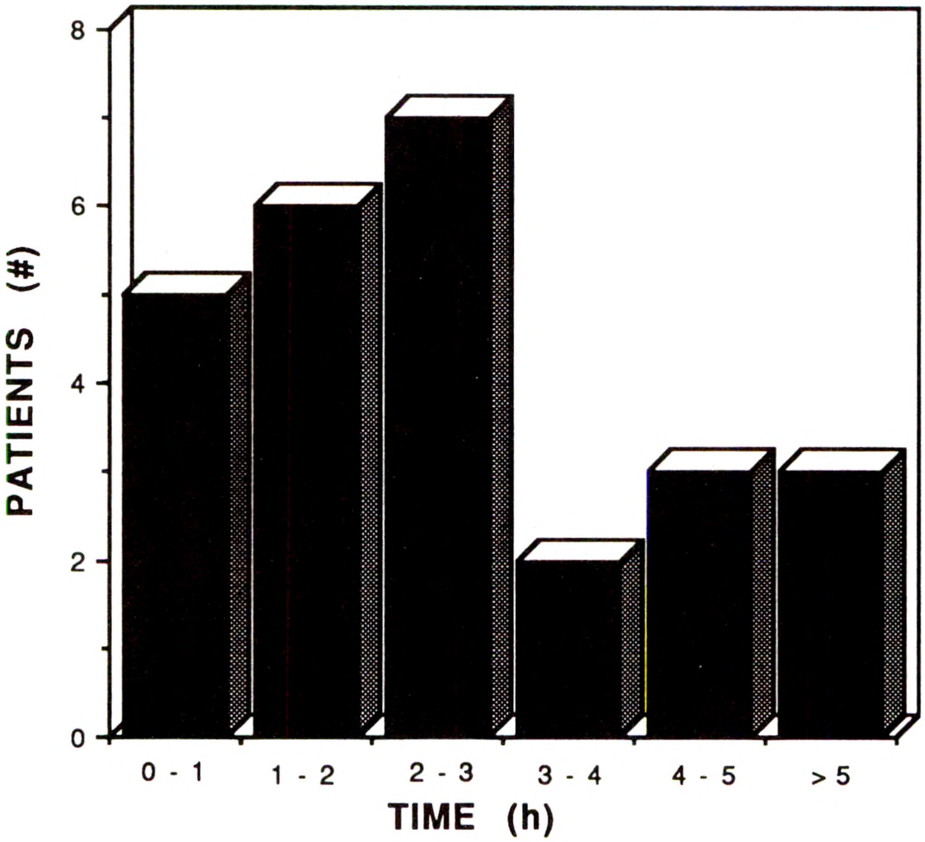

Figure 3. Distribution of patients according to length of surgery. Eighteen of the 26 patients (69%) underwent surgical procedures lasting less than 3 h.

were in this age group ($P < 0.05$). The proportion of intubated patients who had otolaryngologic operations (23%) was three times that of the nonintubated patients (7%) ($P = 0.008$). The median PACU admission score for the intubated group was 5.0 (range, 0–9) in comparison with a median of 7.0 (range, 0–9) for the nonintubated group ($P < 0.001$). Furthermore, 73% (19/26) of the intubations occurred during the months of January through June, whereas only 49% of those not intubated were admitted to the PACU during the same period ($P = 0.016$). All 26 patients were eventually discharged from the hospital without sequelae of these events.

Discussion

Recovery from the residual effects of anesthesia has been associated with substantial risk. Inadequate airway maintenance in particular has contributed significantly to this perioperative morbidity. The 1947 report from the Anesthesia Study Commission of the Philadelphia County Medical Society after 11 yr of study was among the earliest to focus on mortality secondary to anesthesia. In that report, of 307 deaths within 24 h of anesthesia 47% were judged to have been preventable. The need for postanesthesia recovery units was emphasized by the fact that inadequate nursing care along with postoperative respiratory obstruction accounted for 65% of the preventable deaths (4). In a 10-yr survey of death attributable to anesthesia published in 1978, Harrison reported that complications of tracheal intubation and respiratory inadequacy after neuromuscular blockade were alone responsible for 36% of deaths occurring within 24 h of anesthesia (1). In 1980, expansion of the concept of operative mortality to include deaths occurring well beyond the first 24 postoperative hours revealed that respiratory insufficiency accounted for 22% of the deaths to which anesthesia contributed primarily; insufficient fluid balance, cardiac dysfunction, and aspiration accounted for 51% (5).

These early surveys focused on mortality; subsequent efforts have been aimed at understanding the nature of the nonfatal but often equally life-threatening anesthesia-related complications (3,6–11). Improvements in postanesthesia care ranging from increased physician awareness and the introduction of skilled nursing personnel to advances in monitoring and establishment of quality assurance programs have occurred since the early days of a PACU. The effects of pulse oximetry and information

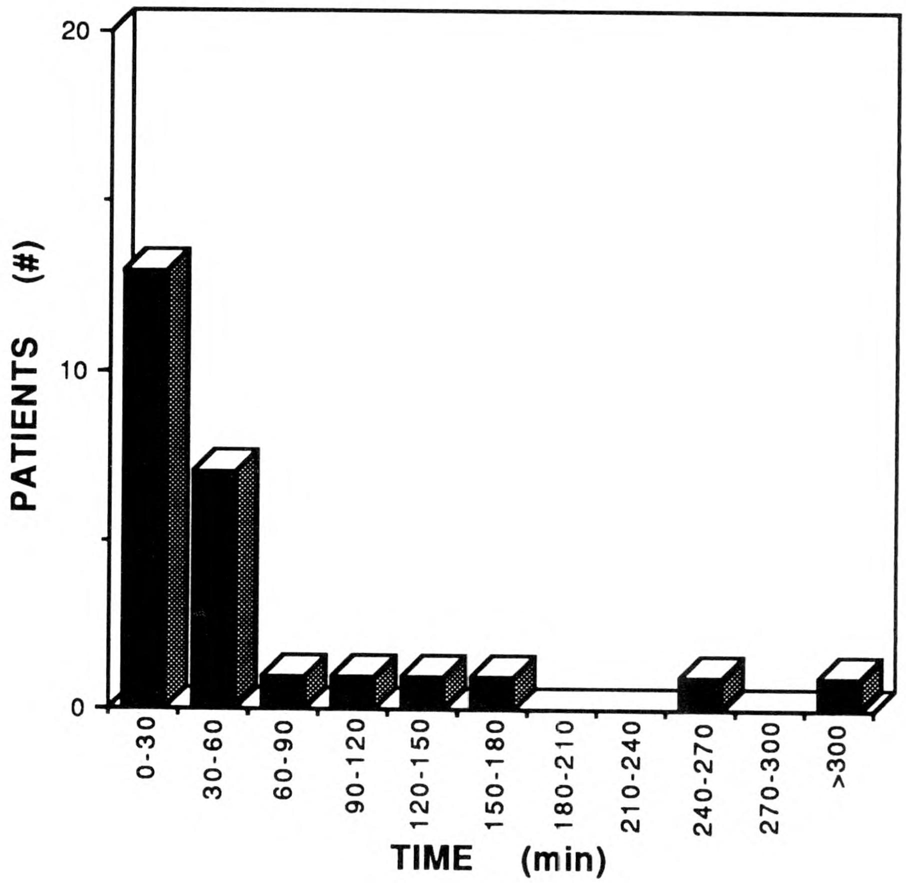

Figure 4. Time to intubation while in PACU. Twenty of the 26 intubations occurred within 1 h of extubation and/or admission to the PACU.

Table 1. Emergency Intubation in the Postanesthesia Care Unit[a,b]

Predominant reason for intubation[c]	*n*
Airway obstruction related to head and neck pathology	
Bleeding at the surgical site	2
Tracheal compression from a goiter[d]	1
Unexpected laryngeal edema	2
Laryngeal edema from prolonged upper airway surgery[d]	1
Posttonsillectomy pulmonary edema	1
Excessive sedation or anesthetic agent[d]	6
Inappropriate fluid management[d]	6
Persistent muscle relaxant effect[d]	3
Miscellaneous (sepsis, transfusion reaction, bronchospasm, inappropriate intubation[d])	4

[a] *n* = 13,593 consecutive patients.
[b] Intubation rate = 0.19%.
[c] Total number of patients intubated = 26.
[d] Intubation as a consequence of anesthetic management.

feedback on PACU care have also recently been studied (12). Despite these advances, the PACU remains a patient care area associated with a significant morbidity rate, with an overall complication rate ranging from 17% to 30% (3,8).

The incidence of emergency intubation in this large series (0.19%) is similar to that in other reports (8,13). Previous studies, however, have been limited in size (*n* = 443) (8) or have discussed intubations in the PACU only as they related to an increased incidence after specific otolaryngologic procedures (panendoscopy, laryngeal biopsy) (13). The etiology of all tracheal intubations in the PACU and the relationship of these intubations to intraoperative anesthetic management have never been addressed. In our study, although there was no relationship between intubation and gender, anesthetic technique, or anesthetic agent, it is of interest that 14 of the 26 intubations (54%) occurred in those more than 60 yr of age. Also of note, 12 patients (46%) were classified as ASA physical status I or II, and an additional 12 (46%) were classified as ASA physical status III. Eight of these patients underwent emergent surgery. Similar patterns with regard to mortality and age, ASA classification, or emergent nature of surgery have been reported earlier (1,5). Contrary to what we had expected, 18 intubations (69%) occurred in surgical procedures lasting less than 3 h, and, in contrast to earlier reports, we were unable to correlate the occurrence of intubations with the level of training achieved by the anesthesiologist (14). Seventy-three percent of the intubations, in fact, occurred during the months of January through June (the second half of the academic year) perhaps reflecting greater resident independence and/or less resident supervision. Twenty intubations (77%) occurred within 1 h of admission to the PACU and/or extubation—a point in time when maximal subglottic pressure and laryngeal edema postextubation is said to occur (15).

Although the patients requiring intubation in the PACU were a very small fraction of the total number of patients admitted, we believe that they demonstrate examples of error in judgment by the care team. It is clear that the nine (9/26) patients with persistent sedative and muscle relaxant effects as well as the patient who was unnecessarily intubated are examples of errors in management. Although it is true that the immediate recovery period is when the residual effects of anesthetics are known to persist, the vast majority of the PACU population are not so severely compromised as to require tracheal intubation. The 8.3% incidence of airway support using means other than an endotracheal tube perhaps portrays the residual effects of anesthetic agents associated with lesser degrees of airway compromise. The fact that seven of the nine patients who required intubation because of persistent sedative and muscle relaxant effects were intubated within 35 min of admission to the PACU, and the fact that this group had a lower median PACU admission score, leads us to ask whether they should have been transported to the PACU without first establishing ventilatory adequacy.

The five (5/26) patients with pulmonary edema must also be regarded as having excessive fluid replacement along with an erroneous estimation of cardiac reserve or coexisting illness. Similar to Cooperman's earlier finding, 60% (3/5) of the instances of pulmonary edema in our series occurred within 1 h of termination of anesthesia (16). Of these five instances, two were clearly due to overinfusion of fluids. The remaining three instances reflected relative overinfusions combined with underestimation of coexisting cardiac or renal disease and changes such as termination of positive pressure ventilation plus the occurrence of hypertension and tachycardia associated with pain at cessation of general anesthesia. Although the role of coexisting disease is difficult to define in any intraoperative or postoperative complication, our review revealed that it is primarily failure to appreciate the extent of coexisting disease that resulted in increased patient morbidity. Similarly, the one patient who was volume-depleted reflected a gross underestimation of fluid balance.

Among the seven patients with upper airway obstruction related to head and neck pathology was one in whom the extent of a goiter was unappreciated by the anesthesia care team. The patient in whom postoperative laryngeal edema should have been anticipated based on the nature of the surgery, along with the two patients with bleeding at the operative site, reflect errors in management as well. This group of seven patients serves to illustrate the well-known fact that increased airway manipulation leads to an increased incidence of reintubation. Hill has demonstrated that patients undergoing laryngoscopy (1.2%) and panendoscopy (3%) have significantly higher rates of postoperative tracheal intubation. In his series, 92% of the patients intubated underwent a laryngeal biopsy (13).

In conclusion, physical status of the patient and the judgment and skill of the physician have often been viewed as the prime determinants of operative mortality (17). Although this study may be limited by its retrospective nature and by the fact that many individuals were reporting the data, it does reveal that despite an extremely low incidence of emergency intubation in a heterogeneous group of patients admitted to the PACU, preventable anesthesia and surgical complications accounted for 77% (20/26) of the intubations.

The authors are grateful to Gail Watrous, RN, and the nurses of the PACU for their help with this study.

References

1. Harrison GG. Death attributable to anesthesia: a 10-year survey (1967–1976). Br J Anaesth 1978;50:1041–6.
2. Demling RH, Read T, Lind LJ, Flanagan HL. Incidence and morbidity of extubation failure in surgical intensive care patients. Crit Care Med 1988;16:573–7.
3. Gewolb J, Hines R, Barash P. A survey of 3244 consecutive admissions to the post-anesthesia recovery room at a university teaching hospital (abstract). Anesthesiology 1987;67:A471.
4. Ruth HS, Haugen FP, Grove DD. Anesthesia Study Commission: findings of eleven years' activity. JAMA 1947;135:881–4.
5. Hovi-Viander M. Death associated with anesthesia in Finland. Br J Anaesth 1980;52:483–9.
6. Eltringham RJ, Coates MB, Hudson RBS. Observations on 10,000 patients in the immediate postoperative period. Resuscitation 1982;6:45–52.
7. Cohen MM, Duncan PG, Pope WDB, Wolkenstein C. A survey of 112,000 anaesthetics at one teaching hospital (1975–1983). Can Anaesth Soc J 1986;33:22–31.
8. Zelcer J, Wells DG. Anaesthetic-related recovery room complications. Anaesth Intensive Care 1987;15:168–74.
9. Utting JE, Gray TC, Shelley FC. Human misadventure in anaesthesia. Can Anaesth Soc J 1979;26:472–8.

10. Davies JM, Strunin L. Anesthesia in 1984: how safe is it? Can Med Assoc J 1984;131:437–41.

11. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anesth Analg 1990;70:160–7.

12. Cooper JB, Cullen DJ, Nemeskal R, et al. Effects of information feedback and pulse oximetry on the incidence of anesthesia complications. Anesthesiology 1987;67:686–94.

13. Hill RS, Koltai PJ, Parnes SM. Airway complications from laryngoscopy and panendoscopy. Ann Otol Rhinol Laryngol 1987;96:691–4.

14. Mandel A, Hines R, Barash P. Does length of training impact on post-anesthesia recovery room complication rate? (abstract). Anesthesiology 1988;69:A794.

15. Biller HF, Bone RC, Harvey JE, Ogura JH. Laryngeal edema: an experimental study. Ann Otol Rhinol Laryngol 1970;79:1084–7.

16. Cooperman LH, Price HL. Pulmonary edema in the operative and postoperative period: a review of 40 cases. Ann Surg 1970;172:883–91.

17. Marx GF, Mateo CV, Orkin LR. Computer analysis of post-anesthetic deaths. Anesthesiology 1973;39:54–8.

Clinical Reports

Clinical and Radiologic Evidence of the Epidural Plica Mediana Dorsalis

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Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—dorsal midline band. ANATOMY, EPIDURAL SPACE—dorsal midline band.

The presence of a connective tissue band that divides the epidural space at the dorsal midline is widely accepted (1–5). Its clinical relevance is related to an increase in the incidence of dural puncture and the possibility of unilateral analgesia, as well as to greater difficulty in introducing an epidural catheter. In the present paper we report a case in which dural puncture and unilateral analgesia, together with radiologic imaging, strongly suggested the presence of this midline band.

Case Report

The patient was a 64-yr-old ASA physical status I woman who weighed 75 kg, was 1.55 m tall, and was scheduled for release of knee joint adhesions after a left total knee replacement performed 2 mo before. Epidural analgesia with local anesthetics was decided as the technique of choice. With the patient in the sitting position, a medial approach, attempted at the L3-L4 space with a 18-gauge Tuohy needle using the air loss-of-resistance technique, resulted in a dural puncture. An attempt to identify the epidural space at an upper interspinous space with the same technique produced another dural tap. At this time, the presence of the plica mediana dorsalis was suspected, and a paramedian approach at the left side of the spine was performed to avoid this structure. A catheter was then introduced without difficulty, leaving the 10-cm mark at skin, so that 3–5 cm of the catheter was in the epidural space. The administration of 15 mL of 2% mepivacaine in fractionated doses through the epidural catheter resulted in excellent but unilateral anesthesia of the right leg. A second epidural catheter was then placed, using again a left paramedian approach, and the injection of 10 mL of 2% mepivacaine produced a motor and sensory block of the left lower extremity. When the blockade was reversed, a new dose of 10 mL of the same anesthetic administered through the second epidural catheter resulted in left unilateral analgesia.

An x-ray showed the two catheters correctly placed at the epidural space (Figure 1). Radiologic contrast (Iohexol) introduced through the first catheter resulted in an "unilateral peridurography" of the right side (Figure 2), and the periduragram was completed after introducing contrast material in the second catheter (Figure 3).

In the postoperative period (10–12 h after insertion of the catheters), the patient developed a mild frontal headache that improved with minor analgesics and hydration.

Discussion

We persisted in inducing epidural anesthesia in this patient despite two dural punctures because we think that this is the most safe and comfortable way to provide anesthesia two or three times daily over several days of painful rehabilitative knee exercises postoperatively.

The dorsomedian connective tissue band or plica mediana dorsalis (PMD) was first demonstrated with

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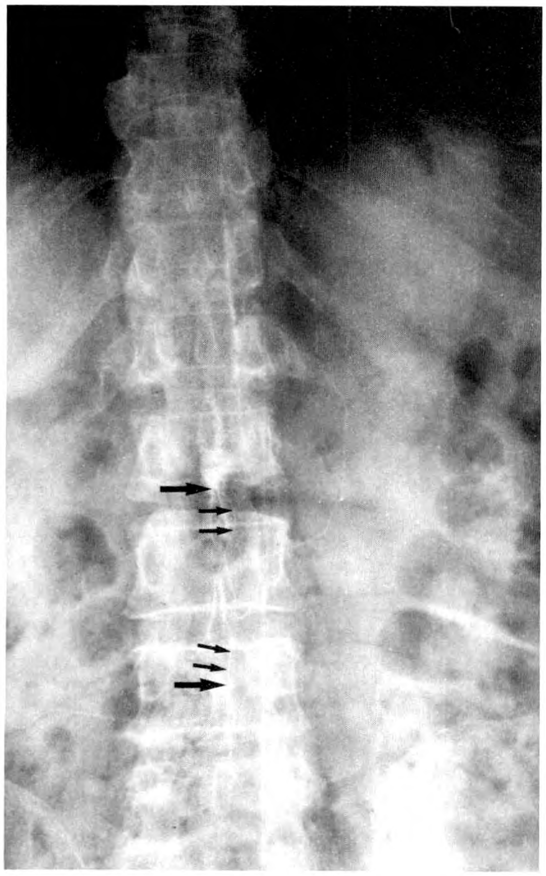

Figure 1. Anterior-posterior x-ray showing both lumbar epidural catheters filled with contrast. The *larger arrows* show the tip of the catheters.

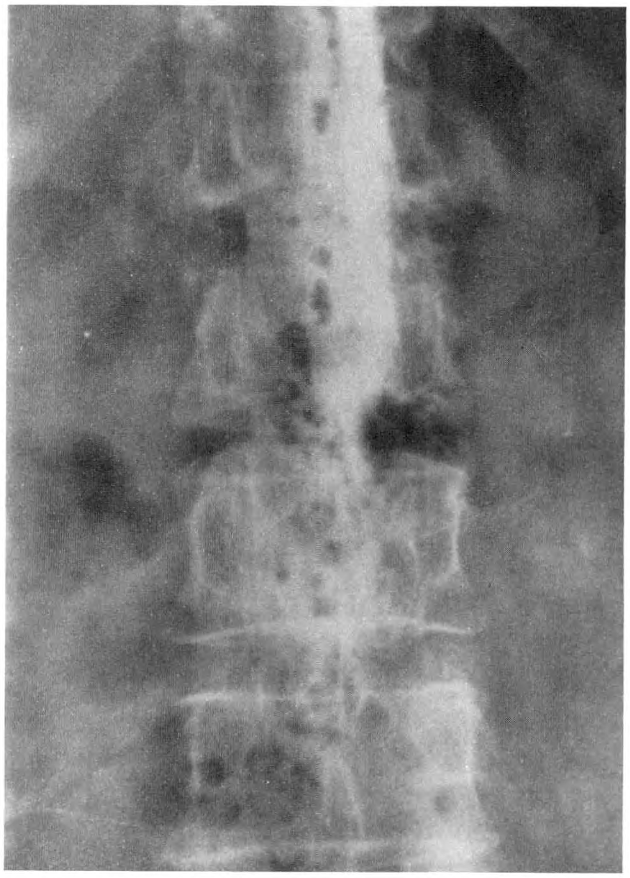

Figure 2. Epidurography obtained with contrast material introduction through the first catheter, showing unilateral distribution of contrast material.

epidurography (1) and later during necropsy (2,3), with epiduroscopy (4) and by computed tomography scan (5). There is no clear agreement regarding its incidence and structural characteristics, probably due to the differences in techniques used to study it and to the fact that the epidural space can be modified when liquid or air are introduced or when enough cerebrospinal fluid is removed to collapse the dura mater (3,6).

The reported frequency of occurrence of the PMD ranges between a few cases reported radiologically or at necropsy (1–3,7) and a 100% incidence in the studies with epiduroscopy (4) and contrast computed tomography scan (5). The PMD binds dura mater and flaval ligament at the dorsal midline; it favors dural puncture because (a) it narrows the epidural space at the midline; (b) it decreases the displacement of the dura when this is pushed by the needle; and (c) it binds the dura to the flaval ligament, making it difficult to feel the loss of resistance. Because this band narrows the epidural space at the midline, it has also been suggested that a catheter can be more easily introduced with a paramedian approach than when the midline is used (8,9). The PMD probably acts as a sagittal barrier for diffusion of the local anesthetics, favoring unilateral analgesia; this fact has been observed clinically and demonstrated with the injection in the epidural space of radiologic contrast materials (10) and resins (2).

In the present report, the presence of the PMD was probably responsible for the repeated dural puncture and unilateral analgesia. The first left paramedial approach resulted in right unilateral anesthesia because the needle probably crossed the midline, so that the tip would be at the right side of the PMD and this midline band would block the diffusion of the local anesthetic to the left side (Figure 4). However, other factors have to be excluded as the cause of unilateral analgesia (11–13), including

1. The slow injection of a small volume of local anesthetic solution with the patient in the lateral position.
2. The passage of the catheter into the paravertebral area, eliminated radiologically in our case.

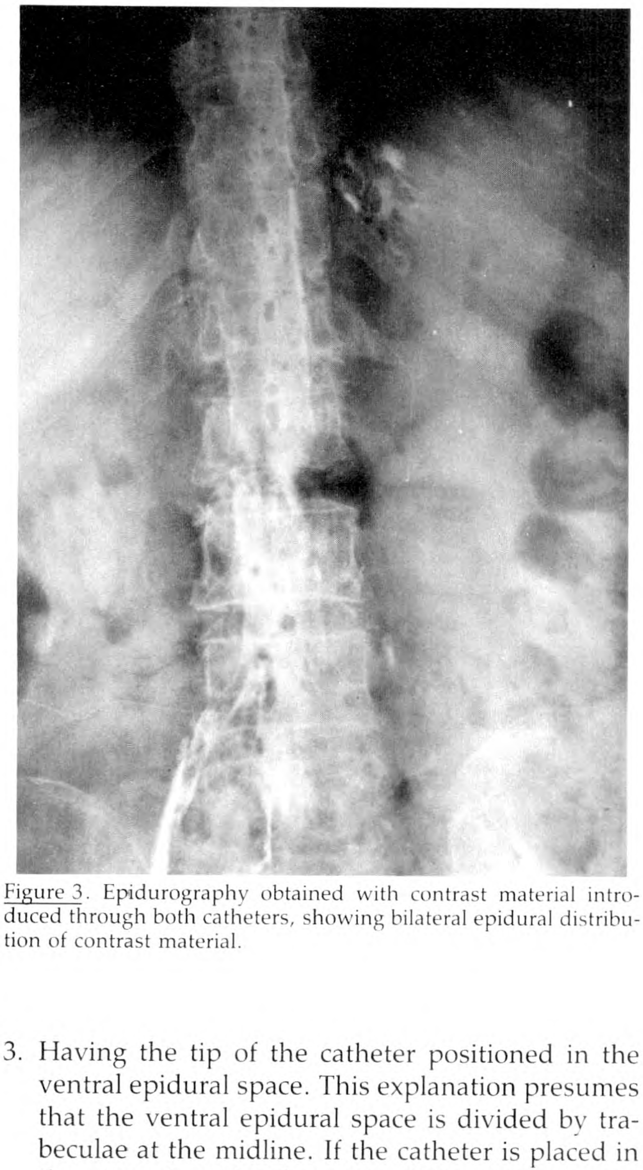

Figure 3. Epidurography obtained with contrast material introduced through both catheters, showing bilateral epidural distribution of contrast material.

3. Having the tip of the catheter positioned in the ventral epidural space. This explanation presumes that the ventral epidural space is divided by trabeculae at the midline. If the catheter is placed in the ventral epidural space, this division would mean that contralateral anesthesia could only be achieved with a retrograde spread of the anesthetic around the circumference of the dura. These trabeculae are described by anatomists (14), but they have not been visualized in subsequent studies (2,5). In our case, radiologic findings showed that the tip of the epidural catheters were not in the ventral epidural space.
4. The catheter could be placed in the lateral epidural space (13), but again radiologic evidence ruled out this possibility in our case.
5. The presence of acquired epidural adhesions due to previous surgery, blood patch, trauma, or neoplasm.

Thus the PMD could favor dural puncture and unilateral anesthesia. How can these problems be avoided? The paramedian approach has been suggested to prevent dural puncture (8,9) and would be the alternative technique if we presume the presence of the PMD. When unilateral analgesia is observed, and if this band is suspected, a paramedian approach could be indicated to place the needle tip at the side of the band ipsilateral to the nerves to be blocked.

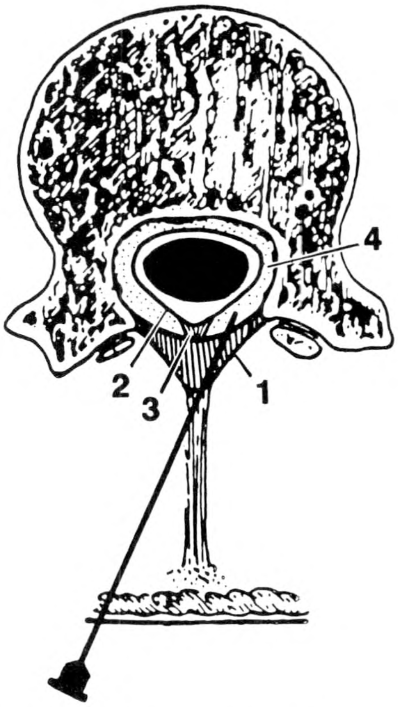

Figure 4. Diagram of how a left paramedial approach can result in right unilateral anesthesia if there is a midline band. 1—ligamentum flavum; 2—dura mater; 3—plica mediana dorsalis; 4—epidural space.

In summary, we present a case in which the presence of a PMD was suspected after a repeated dural puncture. Moreover, it was clinically manifested by unilateral analgesia and was further confirmed radiologically. In our patient a paramedian approach was useful in preventing new dural punctures, as suggested in the literature.

Although there are similar case reports of unilateral analgesia in the literature (15–17), we have found only one with radiologic confirmation that unilaterality was due to PMD (17) and none with the complication of repeated dural puncture.

We thank Professor Margarita M. Puig for her help in editing the manuscript.

References

1. Luyendik W. Canalography. J Belg Radiol 1963;46:236–53.

2. Husemeyer RP, White DC. Topography of the lumbar epidural space. Anaesthesia 1980;35:7–11.
3. Harrison GR, Parkin IG, Shah JL. Resin injection studies of the lumbar extradural space. Br J Anaesth 1985;57:333–6.
4. Blomberg R. The dorsomedian connective tissue band in the lumbar epidural space of humans: an anatomical study using epiduroscopy in autopsy cases. Anesth Analg 1986;65:747–52.
5. Savolaine ER, Pandya JB, Greenblatt SH, Conover SR. Anatomy of the human lumbar epidural space: new insights using CT-epidurography. Anesthesiology 1988;68:217–20.
6. Huson A, Luyendik W, Tielbeek A, Van Zundert A. CT-epidurography and the anatomy of the human lumbar epidural space. Anesthesiology 1988;69:797.
7. Roberson GH, Hatten HP, Hesselink JH. Epidurography: selective catheter technique and review of 53 cases. Am J Roentgenol 1979;132:787–93.
8. Blomberg RG, Jaanivald A, Walther S. Advantages of the paramedian approach for lumbar epidural analgesia with catheter technique. A clinical comparison between midline and paramedial approaches. Anaesthesia 1989;44:742–6.
9. Blomberg RG. Technical advantages of the paramedian approach for lumbar epidural puncture and catheter introduction. A study using epiduroscopy in autopsy subjects. Anaesthesia 1988;43:837–43.
10. Roberson GH, Hatten HP, Hesselink JH. Epidurography: selective catheter technique and review of 53 cases. Am J Roentgenol 1979;132:787–93.
11. Usubiaga JE, Reis AD, Usubiaga LE. Epidural misplacement of catheters and mechanisms of unilateral blockade. Anesthesiology 1970;32:158–61.
12. Narang VPS, Linter SPK. Failure of extradural blockade in obstetrics. A new hypothesis. Br J Anesth 1988;60:402–4.
13. Bromage PR. Continuous epidural analgesia. In: Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:163–93.
14. Testut L, Latarjet A. Anatomía humana. Barcelona: Salvat, 1978.
15. Nunn G, Mackinnon RPG. Two unilateral epidural blocks. Anaesthesia 1986;40:439.
16. Bailey PW. Median epidural septum and multiple cannulation. Anaesthesia 1986;41:881–2.
17. Boezaart AP. Computerized axial tomo-epidurographic and radiographic documentation of unilateral epidural analgesia. Can J Anaesth 1989;36:697–700.

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Electrocautery-Induced Airway Fire During Tracheostomy

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Key Words: ELECTRICAL SYSTEMS, ELECTROCAUTERY—fires. EXPLOSIONS, FIRES—electrocautery.

Although most of the recent attention regarding airway fires has focused on the intraoperative use of the laser, it is important to remember that electrocautery may also serve as a source of ignition during surgery involving the airway and/or oropharyngeal cavity. This subject is mentioned in only a handful of isolated reports in the recent literature (1–3). The following is, we believe, the first case report of an electrocautery-induced fire occurring during an elective tracheostomy.

Case Report

The patient was a 33-yr-old woman with multiple medical problems including steroid-dependent nephritis, acute pancreatitis, and pneumonia complicated by the development of adult respiratory distress syndrome. After 2 wk of mechanical ventilation through an endotracheal tube that would be necessary for an indefinite period, she was brought to the operating room for elective tracheostomy.

Preoperative examination revealed an obese Cushinoid woman, awake and able to follow commands. Pulse rate was 108 beats/min, blood pressure 170/90 mm Hg, temperature 39°C, and respiratory rate 15 breaths/min with an intermittent mandatory ventilation rate of 10 breaths/min. Breath sounds were clear, but distant and not easily auscultated because of the patient's obesity and pulmonary abnormalities. Chest x-ray before surgery revealed bilateral pleural effusions and right lower lobe infiltration. Blood gas tensions included a Paco_2 of 37 mm Hg, Pao_2 of 83 mm Hg, and a pH of 7.40 during intermittent mandatory ventilation rate at a rate of 10 breaths/min with a tidal volume of 500 mL, positive end expiratory pressure of 10 cm H_2O, and an Fio_2 of 40%.

The patient was brought to the operating room, and anesthesia was induced with fentanyl and midazolam. Vecuronium was given for paralysis. Chest compliance was poor, and breath sounds remained diminished. The patient was given 100% oxygen with oxyhemoglobin saturation of 96%–98% by pulse oximetry. Blood gas tensions after induction were Pao_2 323 mm Hg, Paco_2 33 mm Hg, and pH 7.40. The neck was cleansed with povidone iodine, surgical drapes were put in place, and surgery was started. After the neck incision was made, an electrocautery device was used to secure hemostasis. After approximately 15 min, as the electrocautery device was being used, a loud pop was heard, followed by a fire in the surgical field. Moist towels were used to extinguish the flames, and the charred endotracheal tube was removed (Figures 1 and 2) and replaced with a #6.0 Shiley tracheostomy tube. The patient's vital signs remained stable throughout, including oxyhemoglobin saturation, which remained greater than 95% on the pulse oximeter. Flexible bronchoscopy and direct laryngoscopy revealed a thermal injury to the posterior midtrachea involving approximately a 3-cm area extending 50% around the tracheal circumference. The patient tolerated the remainder of the procedure well and was taken back to the intensive care unit in stable condition. Postoperatively, a chest x-ray showed a large right-sided pneumothorax. (In retrospect the preoperative chest x-ray was also consistent with a pneumothorax, but only with a small one.) A chest tube was inserted and suction applied. The patient was followed closely over the next several weeks by both otolaryngologists and anesthesiologists. Bronchoscopy, performed periodically during this time, revealed the posterior tracheal wall to be

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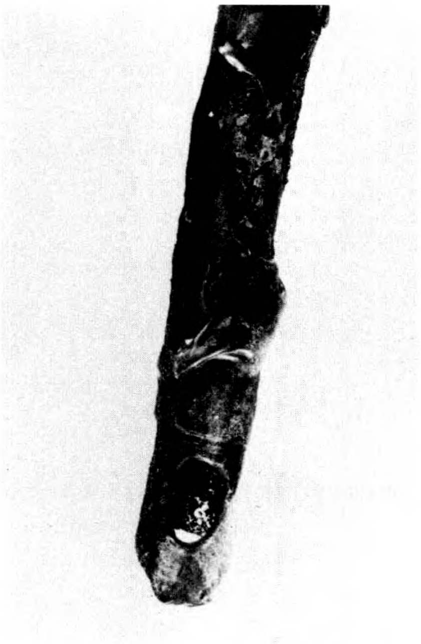

Figure 1. Distal end of endotracheal tube depicting cuff and Murphy eye.

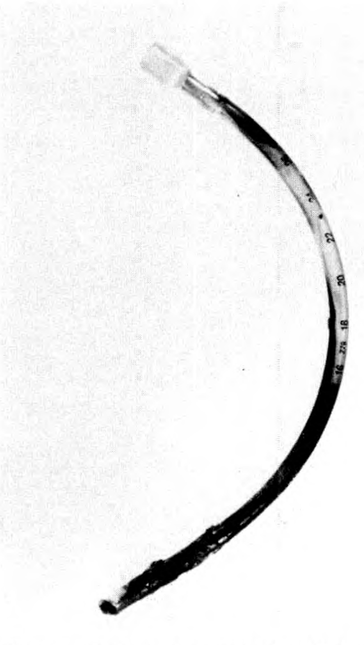

Figure 2. Full view of charred endotracheal tube.

healing without difficulty. Unfortunately, the patient continued with a long and protracted course, including development of hepatic failure and sepsis; she died 1 mo later.

The primary cause of death, determined at autopsy, was attributed to respiratory insufficiency as evidenced by lung abscesses with consolidation and multiple pulmonary emboli.

Discussion

Electrocautery is frequently employed during surgical tracheostomy, specifically in the "cutting mode" for separation of tissues and in the "coagulation mode" for control of bleeding. When used in such a fashion, electrocautery completes the triad required for production of an intraoperative fire, namely (a) a source of ignition (the electrocautery device); (b) a combustible material (the endotracheal tube); and (c) an oxidizing agent (oxygen and/or nitrous oxide) (1,2,4). Surgical tracheostomy, however, is not considered a procedure at high risk for the development of a fire because, theoretically, these three components do not come into contact with one another. This case should put that myth to rest. We believe that, in this instance, the cuff on the endotracheal tube was accidently ruptured by the electrocautery device, exposing the current to an atmosphere of virtually 100% oxygen, thereby leading to ignition of the endotracheal tube.

Prophylactic measures to avoid fires have been recommended during tracheostomies and should be used to guard against the risk of fire during routine tracheostomy. For example, reduction of the concentration of the oxidizing agent can be accomplished by dilution of oxygen with nitrogen (air) and/or helium, both of which reduce combustibility (5–7). (Nitrous oxide on the other hand, enhances combustion.) Next, the source of the ignition must be considered. Comparison of combustibility and resulting tracheal damage from laser-ignited tubes has shown polyvinyl chloride tubes to be more susceptible to ignition and production of tracheal damage than wrapped red rubber tubes in nitrous oxide–oxygen mixtures (8). Whether or not this applies to electrocautery-induced fires is unknown. Based on the available information, however, Shapiro and El-Baz state, "The use of N_2O and O_2 during anesthesia for intraoral, pharyngeal, or laryngotracheal procedures should be avoided completely in favor of air or air-oxygen mixture" (6). And finally, perhaps we should question the use of the electrocautery device at all for this type of procedure, i.e., tracheostomy. After experiencing a fire due to use of electrocautery occurring during transtracheal ventilation for emergency tracheostomy, Bowdle et al. recommend that "electrocautery, especially for cutting, should be avoided if at all possible when the surgical field is immediately adjacent to the oxygen source" (1). Other authors stress the use of bipolar, rather than unipolar, electrocautery, which would thereby minimize the amount of leakage current available (9).

In summary, we recommend the following precautions as a minimum for prevention of fire during elective tracheostomy:

1. Use of oxygen-air and/or helium mixtures to reduce combustibility, if the patient's condition permits.
2. Sparing use of the electrocautery device, if any, at low levels of voltage, particularly as the trachea is exposed during the surgical resection.
3. Use of bipolar rather than unipolar electrocautery for prevention of current leakage.
4. Inflation of the endotracheal tube cuff with saline or water instead of air.

Is this overkill for a procedure such as a simple tracheostomy? Having been burned once, we think not.

References

1. Bowdle TA, Glenn M, Colston H, Eisele D. Fire following use of electrocautery during emergency percutaneous transtracheal ventilation. Anesthesiology 1987;66:697–8.
2. Simpson JI, Wolf GL. Endotracheal tube fire ignited by pharyngeal electrocautery. Anesthesiology 1986;65:76–7.
3. Rita L, Seleny F. Endotracheal tube ignition during laryngeal surgery with resectoscope. Anesthesiology 1982;56:60–1.
4. Perry LB, Gould AB, Leonard PF. "Nonflammable" fires in the operating room. Anesth Analg 1975;54:152–4.
5. Wolf GL, Simpson JI. Flammability of endotracheal tubes in oxygen and nitrous oxide enriched atmosphere. Anesthesiology 1987;67:236–9.
6. Shapiro JD, El-Baz NM. N_2O has no place during oropharyngeal and laryngotracheal procedures (letter). Anesthesiology 1987; 66:447–8.
7. Pashayan AG, Gravenstein JS, Cassisi NJ, McLaughlin G. The helium protocol for laryngotracheal operations with CO_2 laser: a retrospective review of 523 cases. Anesthesiology 1988;68:801–4.
8. Ossoff RH, Duncavage JA, Eisenman TS, Karlan MS. Comparison of tracheal damage from laser ignited endotracheal tube fires. Ann Otol Rhinol Laryngol 1983;92:333–6.
9. Sommer RM. Preventing endotracheal tube fire during pharyngeal surgery (letter). Anesthesiology 1987;66:439.

Caudal Steroid Injection for Treatment of Piriformis Syndrome

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Key Words: PAIN, PIRIFORMIS SYNDROME. ANESTHETIC TECHNIQUES, EPIDURAL—caudal injections in piriformis syndrome.

Piriformis syndrome is a syndrome of low back and leg pain thought to be due to chronic contracture of the piriformis muscle that causes irritation of the sciatic nerve. Yeoman (1) in 1928 first drew attention to the role of the piriformis muscle in sciatica when he proposed that arthritic changes in the sacroiliac joint sometimes produce sciatica by causing an inflammatory reaction of the piriformis muscle and its fascia. It was Robinson (2) who, in 1947, coined the term "pyriformis syndrome."

The piriformis is a flat pyramidal muscle originating from the front of the sacrum, the gluteal surface of the ilium, and the anterior capsule of the sacroiliac joint. It leaves the pelvis through the greater sciatic foramen and inserts into the upper border of the greater trochanter, sharing a common tendon with the obturator internus.

Anatomic studies (3) have shown that in 90% of dissections the undivided sciatic nerve passes out of the greater sciatic foramen below the piriformis muscle (Figure 1a). In 7% of dissections the divisions of the nerve pass between and below the heads of the muscle (Figure 1b), and in 2% the divisions pass above and below the undivided muscle (Figure 1c). Furthermore, a third of the anatomic variations were found to be unilateral. Such intimate association has served to explain sciatic pain based on piriformis contracture in several reviews (4–7).

Diagnosis of piriformis syndrome is made primarily on the basis of history and clinical examination. The incidence is considerably higher in women, with the reported ratio of women to men of 6:1 (8). These patients frequently present with associated symptoms of pelvic pain and/or dyspareunia. Symptoms are usually unilateral but may occasionally be bilateral. It was formerly believed that radiographic investigation did not aid in the diagnosis, but a recent report describes the use of bone scan to demonstrate abnormal uptake in the soft tissues of the pelvis in the distribution of the piriformis muscle (9).

Treatment options described in the literature have included rectal massage (10), rectal diathermy (11), surgical section of the muscle itself (12,13), osteopathic manipulations, and physical therapy (5). Direct injection of the muscle with local anesthetic and steroid (8) has been advocated as being of both diagnostic and therapeutic value. This is usually, however, a painful procedure and not readily accepted by most patients. We have utilized an alternative approach using caudal steroid injection in the treatment of refractory cases of piriformis syndrome. Review of the world literature extending back to 1928 does not indicate prior use of caudal steroids in the treatment of this syndrome.

Patients and Methods

This study was done on the basis of a chart review. Between 1980 and 1989 a total of 12 patients met our criteria for the diagnosis of piriformis syndrome (Table 1). All were women between the ages of 16 and 49 yr (mean, 32 yr).

Duration of the pain at the time of initial presentation ranged from 6 mo to 4 yr (mean, 2 yr). All of the patients had negative radiologic findings and negative electromyographic studies of the muscles innervated by the sciatic nerve roots. Conservative management with nonsteroidal antiinflammatory drugs and physical therapy was unsuccessful. One patient had had direct injection of lidocaine and steroid into the piriformis muscle, with only short-term pain relief.

Caudal injections were performed with patients in the prone position using a 22-gauge 1.3-cm spinal needle. Injection consisted of 60–80 mg of the corticosteroid triamcinolone with 15 mL of 0.25% bupivicaine. The local anesthetic served as a vehicle for the

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Received from the Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan. Accepted for publication August 10, 1990.

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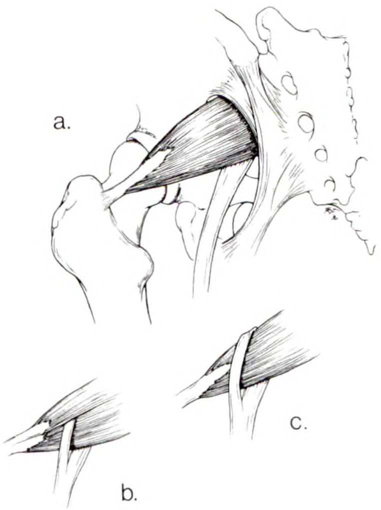

Figure 1. The piriformis muscle and anatomical variations of the relationship to the sciatic nerve. (Adapted from Beaton and Anson [3].)

Table 1. Diagnostic Criteria for Piriformis Syndrome

Good movement of lumbar spine
Positive straight leg raising
Sciatic notch tenderness
Pain and restriction of internal rotation of the thigh
Pain on resisted abduction of the knees with the patient sitting
Presence of trigger point in muscle on affected side by pelvic examination
Negative computed tomography scan

steroid and as an immediate marker for successful caudal blockade.

Results

Seven patients had single injections. Three patients had two injections and two patients had three injections over a period of 3–6 mo. Follow-up time was at least 1 yr for 11 patients; the 12th patient has been followed for a period of 9 mo to date. There were no immediate or late complications.

All patients reported significant pain relief during follow-up, ranging from 9 to 24 mo. Pain relief was assessed by the usual clinical criteria used in our pain clinic. This included the subjective report of the patients who rated their pain on the basis of none, mild, moderate, or severe, as well as objective criteria such as reduced use or discontinuation of analgesics and improved functional capacity. Seven patients reported complete pain relief after a single injection. Five patients reported 25%–75% pain relief after the first injection and complete pain relief after the second and third injections.

Discussion

The close proximity of the sciatic nerve to the piriformis muscle often results in both a diagnostic and a therapeutic dilemma. Complaints of neurologic symptoms with essentially negative neurologic findings and negative electromyographs are confusing. However, the anatomic basis for these neurologic symptoms is now well recognized. The muscle itself is innervated by branches from S1 and S2, which has some bearing on the clinical picture. Thus, although the piriformis syndrome is primarily a myofascial syndrome, it is usually the entrapment of the sciatic nerve that produces the most distressing symptoms.

Injection of the piriformis muscle with local anesthetic and/or steroid has been described in the diagnosis and treatment of this condition. Injection can be made transcutaneously or, if the patient is female, per vaginum using a technique similar to that used in a paracervical block. Both injection techniques require firm pressure on the muscle itself and are always extremely painful for the patient. Furthermore, there is a real risk of direct trauma to the sciatic nerve or portions of the nerve from the needle.

Use of epidural steroids by the lumbar or caudal route is well established in the treatment of low back pain associated with nerve root irritation. Solutions deposited in the caudal epidural space would be expected to diffuse along the nerve root sleeves and hence along the proximal part of the sciatic nerve. We, therefore, believed that caudal steroid injections might be of value in this syndrome, and our results confirm this. Local anesthetic and steroids injected into the caudal space will relieve not only sciatic nerve irritation but also the muscle spasm and pain of piriformis muscle contracture by blocking the innervation of the muscle itself. Gentle stretching exercises used in conjunction with these injections usually result in excellent long-term pain relief.

References

1. Yeoman W. The relation of arthritis of the sacroiliac joint to sciatica. Lancet 1928;ii:1119–22.
2. Robinson D. Pyriformis syndrome in relation to sciatic pain. Am J Surg 1947;73:355–8.
3. Beaton L, Anson B. The sciatic nerve and the piriformis muscle: their interrelation a possible cause of coccygodynia. J Bone Joint Surg 1938;20:686–8.

4. TePoorten B. The piriformis muscle. J Am Osteopath Assoc 1969;69:78–80.
5. Retzlaff E, Berry AH, Haighd AS, et al. The piriformis muscle syndrome. J Am Osteopath Assoc 1974;73:55–63.
6. Steindler A. Differential diagnosis of pain low in the back. JAMA 1938;110:106–13.
7. Wyant GM. Chronic pain syndromes and their treatment. III. The piriformis syndrome. Can Anaesth Soc J 1979;4:305–8.
8. Pace J, Nagle D. Piriformis syndrome. West J Med 1976;124: 435–9.
9. Karl RD, Yedinak MA, Hartshorne MF, et al. Scintigraphic appearance of the piriformis muscle syndrome. Clin Nucl Med 1985;10:361–3.
10. Thiele G. Tonic spasm of the levator ani, coccygeus and piriformis muscles. Trans Am Pract Soc 1936;37:145–55.
11. Sinaki M, Merritt J, Stillwell GK. Tension myalgia of the pelvic floor. Mayo Clin Proc 1977;52:717–22.
12. Freiberg A. Sciatic pain and its relief by operations on muscle and fascia. Arch Surg 1937;34:337–50.
13. Solheim LF, Siewers P, Paus B. The piriformis muscle syndrome. Acta Orthop Scand 1981;52:73–5.

Letters to the Editor

Epileptogenic Foci and Local Cerebral Metabolism

Key Words: BRAIN, GLUCOSE METABOLISM AND EPILEPSY. COMPLICATIONS, EPILEPSY—role of brain metabolism.

To the Editor:

The review articles of Modica et al. (1,2) consider very nicely the clinical and experimental evidence for possible mechanisms by which general anesthetics and drugs used in anesthesia produce seizures or, conversely, have anticonvulsant properties. In this context, the authors point out that the epileptogenic properties of enflurane, narcotic analgesics, and local anesthetics may be reflected by their effects on local cerebral glucose use (LCGU), in particular in areas of the limbic system. In their summary, the authors suggest that in vivo imaging techniques able to detect tissue chemical- or drug-receptor interactions may provide further information about brain areas involved in the action of anesthetic drugs within the central nervous system.

In our opinion, the methodologic constraints and experimental evidence support the view that the autoradiographic ^{14}C-deoxyglucose method (3) does not permit the precise localization of the brain areas mediating the convulsive effects of drugs. Local cerebral glucose use studies require steady-state conditions, and this is obviously not possible in the case of seizures, as pointed out by Young et al. (4), and by Collins et al. in their study of focal motor seizures (5). In addition, because LCGU studies do not allow the differentiation between central nervous system regions primarily affected by drugs and central nervous system areas secondarily recruited (6), some of the observed LCGU changes may not reflect the sites of origin of the epileptic discharges but rather the spreading of the abnormal electrical activity. Finally, drugs with proconvulsant effects do not necessarily produce a pattern of LCGU alterations distinctively different from the patterns associated with drugs devoid of this effect. In fact, brain areas with increased LCGU proposed by Myers and Shapiro as epileptogenic foci during enflurane anesthesia (7), and by Ingvar and Shapiro after lidocaine administration (8), are also metabolically activated by anesthetics lacking excitatory activity such as halothane (9) and isoflurane (10).

Therefore, caution is mandatory in interpreting LCGU findings: so far no studies have been able to demonstrate a unique relation between the observed metabolic variations and the mechanisms of anesthesia or anesthesia-related phenomena.

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References

1. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part I). Anesth Analg 1990;70:303–15.
2. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part II). Anesth Analg 1990;70:433–44.
3. Sokoloff L, Reivich M, Kennedy C, et al. The (^{14}C)deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 1977;28:897–916.
4. Young ML, Smith DS, Greenberg J, Reivich M, Harp JR. Effects of sufentanil on regional cerebral glucose utilization in rats. Anesthesiology 1984;61:564–8.
5. Collins RC, Kennedy C, Sokoloff L, Plum F. Metabolic anatomy of focal motor seizures. Arch Neurol 1976;33:536–42.
6. Dam M, Pizzolato G, Ricchieri GL, Battistin L. Metabolic fingerprints of neuroactive drugs. In: Battistin L, Gerstenbrand F, eds. Aging brain and dementia. New trends in diagnosis and therapy. New York: Wiley-Liss, 1989:319–36.
7. Myers RR, Shapiro HM. Local cerebral metabolism during enflurane anesthesia: identification of epileptogenic foci. Electroencephalogr Clin Neurophysiol 1979;47:153–62.
8. Ingvar M, Shapiro HM. Selective metabolic activation of the hippocampus during lidocaine-induced preseizure activity. Anesthesiology 1981; 54:33–7.
9. Savaki HE, Desban M, Glowinski J, Besson MJ. Local cerebral glucose consumption in the rat. I. Effects of halothane anesthesia. J Comp Neurol 1983;213:36–45.
10. Ori C, Dam M, Pizzolato G, Battistin L, Giron GP. Effects of isoflurane anesthesia on local cerebral glucose utilization in the rat. Anesthesiology 1986;65:152–6.

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In Response:

Ori et al. correctly point out limitations in using the 2-deoxyglucose autoradiograph method to assess pro- or anticonvulsant effects of anesthetic agents. As an example, they point out that the requirement of steady-state conditions is not attainable during seizures. However, the steady-state requirement during the period of observation (i.e., from injection of the ^{14}C-deoxyglucose to killing the animal) is only necessary for determination of the absolute regional glucose metabolic rate. Useful information regarding relative regional blood flow, and by inference, the relative regional metabolic activity, can be obtained under a non-steady-state condition (1).

The limitation of the 2-deoxyglucose autoradiograph method is more a problem of temporal resolution. Because the final autoradiographic intensity depends on the accumulation of 2 deoxyglucose-6-phosphate over the duration of the observation period, the resulting image is an indication of the time-averaged relative metabolic rate (1). Such a technique may not be suitable for examining the proconvulsant properties of anesthetic agents, which may only transiently induce neuronal hyperexcitability before attaining cerebral silence.

Other imaging methods with enhanced temporal resolution, such as positron emission tomography (2,3) and single-photon emission computed tomography (4,5), have been successfully used in metabolic mapping of epileptic patients. The application of similar methods in patients undergoing anesthesia may provide greater understanding of anesthetic actions in vivo. We agree with Ori et al. that caution is mandatory in interpreting the local cerebral glucose use findings. However, caution resides in understanding the limitations of the methods and not in the basic concept of using imaging techniques to gain an in-depth understanding of the in vivo effects of anesthetics and analgesics on the central nervous system.

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References

1. Collins RC, Kennedy C, Sokoloff L, Plum F. Metabolic anatomy of focal motor seizures. Arch Neurol 1976;33:536–42.
2. Engel J Jr. The use of positron emission tomographic scanning in epilepsy. Ann Neurol 1984;15(Suppl):S180–9.
3. Hosokawa S, Kato M, Otsuka M, et al. Positron emission tomography in epilepsy: correlative study. Jpn J Psychol Neurol 1989;43:349–53.
4. Magistretti L, Uren RF, Parker JA, Royal HD, Front D, Kolodny GM. Monitoring of regional cerebral blood flow by single photon emission tomography of 1231-N-isopropyl-iodoamphetamine in epileptics. Ann Radiol 1983;26:68–71.
5. Konishi T. Regional cerebral blood flow in epileptic foci using [I-123] IMP-SPECT. Jpn Psychol Neurol 1989;43:355–60.

An Alternative Explanation for Esophageal Perforation During Neonatal Resuscitation: Hazards of Nonregulated Wall Suction

Key Words: ANESTHESIA, OBSTETRICAL. EQUIPMENT, SUCTION—neonatal.

To the Editor:

Topsis et al. describe three cases of traumatic esophageal perforation complicating neonatal resuscitation (1). They emphasize that oropharyngeal suctioning and endotracheal intubation need to be performed skillfully by experienced personnel. They mention regulated wall suction but do not provide detailed guidelines. Recommendations for oropharyngeal suctioning of the neonate are that suction pressures should be 60–80 mm Hg and should not exceed 100 mm Hg (2). In the delivery room, suction pressure can be up to 200 mm Hg. Excessive suction pressure may have been overlooked as a possible cause of traumatic esophageal perforations in these cases.

The report by Topsis et al. implies that it is routine at their institution to use a suction catheter to remove oropharyngeal secretions from the newborn at delivery. Cordero and Hon demonstrated the hazards of inducing bradycardia with this practice (3). For this reason, the American Heart Association and the American Academy of Pediatrics advise against routine use of a suction catheter to remove oropharyngeal secretions. Use of a suction catheter is reserved for meconium-stained fluid, for copious secretions, and for facilitated visualization of the glottis when intubation is indicated (2).

In case 1 of the study by Topsis et al., bradycardia occurred with oropharyngeal suctioning that had been employed in the absence of the usual indications for its use. Use of a bulb syringe, in accordance with American Heart Association recommendations, would have avoided even the opportunity for traumatic esophageal perforation. In cases 2 and 3, the proper-sized endotracheal tubes and suction catheters were employed. These infants were born in the presence of meconium-stained amniotic fluid. Pediatricians used suction catheters in both cases, but there is no report of the intensity of suction. With meconium-stained amniotic fluid, obstetricians perform oropharyngeal suctioning as part of the combined obstetric and pediatric approach to meconium-stained neonates (4). In neither of these cases are details of obstetric suctioning provided. There is increasing reluctance by obstetricians to perform Delee suctioning by mouth because of fears of acquiring HIV infection or hepatitis. There is the possibility that the obstetricians in the cases described by Topsis and associates employed nonregulated wall suction, 200 mm Hg, which could have caused traumatic esophageal perforation. Obstetricians need to remember to employ regulated suction below 100 mm Hg whenever they suction the neonatal oropharynx. This is especially true at cesarean section, when the standard operative maximum wall suction might inadvertently be used to suction the neonatal oropharynx and trauma might be induced. There is no easy way to know during sections if suction is causing esophageal trauma because of the usual blood-stained amniotic fluid at cesarean delivery.

Careful intubation of the newborn by skilled personnel is fundamentally important. Routine use of the bulb syringe and use of regulated suction only when indicated, and always below 100 mm Hg, are also important to avoid traumatic esophageal perforation in neonates.

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References

1. Topsis J, Kinas HY, Kandall SR. Esophageal perforation—a complication of neonatal resuscitation. Anesth Analg 1989;69:532–4.
2. Bloom RS, Cropley C. Textbook of neonatal resuscitation. Dallas, Texas: American Heart Association, 1987: Lesson 2, 12–7.
3. Cordero L Jr, Hon EH. Neonatal bradycardia following nasopharyngeal stimulation. J Pediatr 1971;78:441–7.
4. Carson BS, Losey RW, Bowes WA, Simmons MA. Combined obstetric and pediatric approach to prevent meconium aspiration syndrome. Am J Obstet Gynecol 1976;126:712–5.

Parametric Statistics for Evaluation of the Visual Analog Scale

Key Words: STATISTICS, PARAMETRIC. MEASUREMENT TECHNIQUES, VISUAL ANALOG SCALES.

To the Editor:

Visual analog scales (VASs) are widely used to investigate patients' assessments of recovery after anesthesia. There has been much discussion as to whether parametric or nonparametric techniques are most appropriate for statistical analysis of the VAS. Information from the literature on psychological testing supports the use of parametric techniques.

One issue is whether the VAS represents ordinal, discontinuous data or interval, continuous information. An ordinal scale connotes simple rank-ordering of results, with values usually specified by numbers. An interval scale connotes equal distance between unit values. Most psychological tests such as the VAS provide more information than simple rank-ordering, but equality of units cannot be assured (1). The test data thus lie somewhere between ordinal and interval values.

According to several statistical sources on psychological tests, the parametric (*F* and *t*) techniques are applicable for psychological test data that do not represent clearly interval values (1–3). The use of ordinal versus interval data does not alter the risks of type I and type II errors when statistical inferences are made with parametric tests. Use of nonparametric techniques, however, may increase the likelihood of type II errors (1).

Another issue is whether the VAS data need to be normally distributed for parametric tests to be appropriate. The means of samples of a population (sampling distribution) tend to be normal independent of the underlying population distribution, according to the Central Limit Theorem, and again parametric tests apply (4). Calculations have been done to assess the impact of specifically disregarding the assumptions underlying parametric tests, using different combinations of population distribution shapes, sizes, and variances (5). Sampling from rectangular distributions had negligible effects on the percentage of *t*'s reaching the 0.05 and 0.01 significance levels. Even sampling from a J-shaped distribution produced minimal error in inference.

Maxwell (3) has validated the use of parametric statistics specifically for VAS analysis.

In summary, the VAS represents data that, although not clearly interval values, are most appropriately analyzed by parametric techniques. These techniques permit statistical inferences without altering the risk of type I and type II errors, whereas use of nonparametric techniques may increase the likelihood of type II errors.

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References

1. McNemar Q. Psychological statistics. New York: John Wiley, 1962:374–6.
2. Anderson NH. Scales and statistics: parametric and nonparametric. Psychol Bull 1961;58:305–16.
3. Maxwell C. Sensitivity and accuracy of the visual analog scale. Br J Clin Pharmacol 1978;6:15–24.
4. Colton T. Statistics in medicine. Boston: Little, Brown, 1974:101–2.
5. Boneau CA. The effects of violations of assumptions underlying the *t* test. Psychol Bull 1960;57:59–64.

Vasodilator-Induced Femoral-to-Radial Pressure Gradient After Cardiopulmonary Bypass

Key Words: BLOOD PRESSURE, FEMORAL—radial gradient. ANESTHESIA, CARDIOVASCULAR—femoral-radial pressure gradient.

To the Editor:

Maruyama and coworkers (1) report that the infusion of nitroglycerin and nicardipine during cardiac surgery significantly increased the incidence, magnitude, and duration of the pressure difference between femoral and radial arteries after cardiopulmonary bypass. These data affirm the contention by Pauca et al. (2) that reduction of peripheral vascular resistance is the main cause for this gradient. Such reduction in resistance does not, however, necessarily require vasodilation, as the authors state; reduced viscosity associated with hemodilution also significantly reduces peripheral vascular resistance, according to Pouiseuille, even in the absence of any vasodilation (3).

Maruyama et al. report that there was no statistically significant difference between femoral and radial artery pressure in patients not receiving vasodilators. However, this lack of statistical significance resulted mainly from the large dispersion of the individual measurements; as can be seen in Figures 1 and 2 of their report (1), several patients did indeed have increases in pressure gradient after bypass. This is in agreement with previous reports (4) that have shown that this gradient is a frequent, but not a constant, finding. The most important lesson from the work of Maruyama et al. is that because of the infusion of potent vasodilators, an alteration that was found only in some patients became a constant, predictable response. This observation is, in my opinion, an important step toward understanding the pathophysiology of this phenomenon, which, I have suggested, results from the particular physical and rheological properties of blood and hemodilution in the microcirculation (3).

If it is true that low resistance to blood flow due to reduced viscosity underlies the aortic-to-radial pressure difference (3), it remains unexplained why it was observed only in some patients, even though hemodilution was used in all of them. It may be hypothesized that compensatory increases in cardiac output and vasoconstriction may occur in many, but not in all, patients; the administration of vasodilators would block vasoconstriction, thus increasing the frequency and duration of this pressure difference. The effect of vasodilators would be to "unmask" the underlying effect of hemodilution, while at the same time preventing the normal compensatory vasoconstrictive adaptation from taking place. If vasodilators were solely responsible for this pressure gradient, as Maruyama et al. suggest, disproportionate decreases of radial artery pressure would be seen frequently in the wards in patients under nitroglycerin therapy, which, to my knowledge, is not the case.

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References

1. Maruyama K, Horiguchi R, Hashimoto H, et al. Effect of combined infusion of nitroglycerin and nicardipine on femoral-to-radial arterial pressure gradient after cardiopulmonary bypass. Anesth Analg 1990;70: 428–32.
2. Pauca AL, Hudspeth AS, Wallenhaupt SL, et al. Radial artery-to-aorta pressure difference after discontinuation of cardiopulmonary bypass. Anesthesiology 1989;90:935–41.
3. Urzua J. Aortic to radial arterial pressure gradient after bypass (letter). Anesthesiology 1990;73:191.
4. Gravlee GP, Brauer SD, O'Rourke MF, Avolio AP. A comparison of brachial, femoral and aortic intra-arterial pressures before and after cardiopulmonary bypass. Anaesth Intensive Care 1989;17:305–11.

Interpreting Expired CO_2 Waveforms

Key Words: CARBON DIOXIDE, EXPIRED—waveform.

To the Editor:

In their recent exchange of opinion in their letters to the editor regarding the role of ventilation/perfusion (V/Q) distributions in the slope of the alveolar portion of the CO_2 elimination waveform, Cruz (1) and Benumof (2) have touched on an important contradiction of the sequential emptying theory.

In erect humans, specific ventilation (volume of inspired gas/unit lung volume) is lowest at the apex of the lung and highest at the base of the lung (3). The inspiration of a single breath of 100% O_2 in a patient breathing air should therefore result in a nitrogen concentration that is lowest at the base and highest at the apex of the lung. On exhalation the resulting N_2 expirogram has a positive alveolar slope, i.e., during phase 3 of exhalation the N_2 concentration increases with time and/or exhaled volume (4). The sequential emptying theory can explain the positive slope by postulating that alveolar gas from the base of the lung (with the lowest N_2 concentration) empties first, followed by the gas from mid-lung, and then by gas from the apex (with the highest N_2 concentration).

Ventilation/perfusion ratios, however, are distributed in the lung of upright humans such that lung units with the lowest V/Q ratios are at the base and units with the highest V/Q ratios are at the apex (3). If these lung units empty sequentially from base to apex, the slope of phase 3 of the CO_2 expirogram should be negative (i.e., CO_2 concentration should decrease with time or exhaled volume), which is clearly not the case—the slope of phase 3 for CO_2 in normal erect humans is always positive. Thus, the multicompartment sequential emptying theory does not explain the slope of phase 3 for both CO_2 and N_2 simultaneously in a normal subject (5).

It is refreshing to see this long-standing controversy aired in the anesthesia literature because anesthesiologists represent the only clinical specialty using capnography in daily practice. Monitoring of the CO_2 waveform has become routine and undoubtedly contains a wealth of information about pulmonary structure and function, including blood and gas flow distribution, and acinar morphometry (5). A deeper understanding of gas transport in the lung will ultimately provide a more informed interpretation of the CO_2 expirogram.

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References

1. Cruz JC. What is the meaning of the expired CO_2 waveform (letter)? Anesth Analg 1990;70:675–6.

2. Benumof JL. What is the meaning of the expired CO_2 waveform (reply to letter)? Anesth Analg 1990;70:675–6.
3. West JB. Ventilation/blood flow and gas exchange. 3rd ed. Oxford: Blackwell Scientific, 1977:15–31.
4. Saidel GM. Lewis SM. Distribution of ventilation. In: Chang HK, Paiva M, eds. Respiratory physiology: an analytic approach. New York: Marcel Dekker, 1989:195–237.
5. Scherer PW, Neufeld GR, Aukburg SJ, Hess GD. Measurement of peripheral bronchial cross section from single breath gas washout. J Biomech Eng 1983;105:290–3.

A Hazardous Defect in a Humidifier

Key Words: EQUIPMENT, HUMIDIFIER—obstruction.

To the Editor:

There have been few reports on accidents during general anesthesia related to the use of humidifier equipment (1,2). We recently experienced a previously unreported but potentially dangerous instance of a defect in a Thermo Vent 600 humidifier (Portex Limited). The defect in the humidifier consisted of a complete obstruction of the proximal hole (Y-piece side) by a thin plastic membrane of the same material as that of the body, although the distal hole (on the patient's side) was patent (Figure 1). The patient could not be ventilated immediately after endotracheal intubation after administration of the regular induction doses of thiopental and succinylcholine. Because mechanical airway trouble was initially suspected, we immediately reintubated the trachea using another endotracheal tube. General causes of airway trouble, such as endotracheal tube obstruction, anesthesia breathing circuit trouble, and bronchospasm, were all ruled out. Finally, the humidifier was identified as the culprit because, when we checked the anesthesia machine system, the humidifier was not attached to the anesthesia circuit.

It has been our practice to insert humidifiers between the elbow of the anesthesia circuit and the endotracheal tube immediately after endotracheal intubation without checking them. If we had checked the circuit system when it was attached to the humidifier, this problem would have been avoided. We, therefore, recommend that the preanesthetic machine be checked with the humidifier attached if there is any intention of using the humidifier during the operation. We have obtained assurance from the manufacturer that better inspection and pressure tests are being instituted to prevent production of such defective humidifiers. Even so, anesthesia circuits should still be checked preanesthetically with humidifiers in circuit if they are to be used later on.

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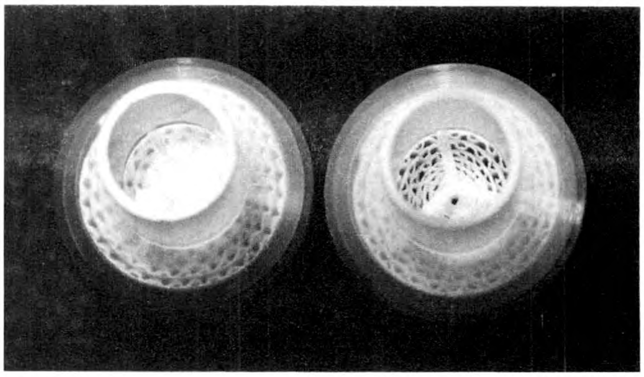

Figure 1. Defective humidifier (*left*) with a thin plastic membrane obstructing the proximal limb in comparison with a normal humidifier (*right*).

References

1. Slee TA, Palvin EG. Failure of low pressure alarm associated with the use of a humidifier. Anesthesiology 1988;69:791–3.
2. Prados W. A dangerous defect in a heat and moisture exchanger. Anesthesiology 1989;71:804.

In Response:

Portex is a responsible manufacturer of single-use medical devices and as such applies rigorous controls to product design, manufacture, and quality.

All Thermovent heat and moisture exchanger housings are now tested to confirm a free flow of gases before assembly.

As the authors state, it should be standard practice to check the performance of equipment before use, particularly when assembly, or use in combination, of several separate products is involved. We endorse this view.

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Intralipid Solution Mistakenly Infused Into Epidural Space

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—inadvertent intralipid injection.

To the Editor:

Epidural infusions of narcotics are routinely used in our institution for management of postoperative pain. Our recent discovery of a patient who had accidently received 300 mL of intralipid total parenteral nutrition solution via his epidural catheter points out one potential complication of this usually uneventful therapy.

A 21-yr-old man with ulcerative colitis underwent a total colectomy. Postoperative pain control was begun with intravenous morphine using a patient-controlled analgesia device. The patient was unable to obtain satisfactory pain relief, and we were consulted. A lumbar epidural catheter was placed, and he received excellent analgesia after 100 μg of fentanyl was injected into the epidural space. A continuous epidural infusion of preservative-free morphine at 1.0 mg/h was then begun using a standard intravenous infusion set connected to the epidural catheter tubing. The tubing and intravenous infusion pump was labeled with bright green "EPIDURAL CATHETER" tags. He remained nearly pain-free for the next 24 h. It was then discovered that an intravenous infusion of intralipid total parenteral nutrition solution had been "piggy-backed" onto the intravenous tubing leading to the epidural catheter. The label covering one of the side ports on the infusion set tubing had apparently been lost. Approximately 300 mL of intralipid solution had been infused at a rate of 60 mL/h. The epidural catheter was removed from the patient. The catheter insertion site appeared normal and was not painful to palpation. Daily visits failed to reveal any neurological deficits caused by this unusual infusion. The epidural site remained normal.

We know of no reports of a similar accidental epidural intralipid infusion. This represents one of the numerous possible complications of epidural infusion therapy. We recommend careful labeling of epidural tubing and infusion pumps, and, where possible, use of infusion sets without side ports that could potentially allow foreign substances into the epidural space.

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A Simple Chin-Support Device During Face Mask Anesthesia

Key Words: AIRWAY, MAINTENANCE.

To the Editor:

To maintain the airway and give the anesthesiologist a free pair of hands for other tasks, a chin-lift device is sometimes used in conjunction with a head harness for mask anesthesia. A padded tongue depressor or reversed Guedel airway (1) has been used for this purpose. The flexible, reusable rubber Guedel airway is no longer available in many hospitals, and, furthermore, additional chin support is often required with these devices to prevent the tongue from falling back and occluding the laryngeal inlet. Lyew (2) described a method by which the ends of the chin support are suspended from a rigid screen using tape. This is a somewhat cumbersome assembly and would require readjustment should the patient be moved on the operating table.

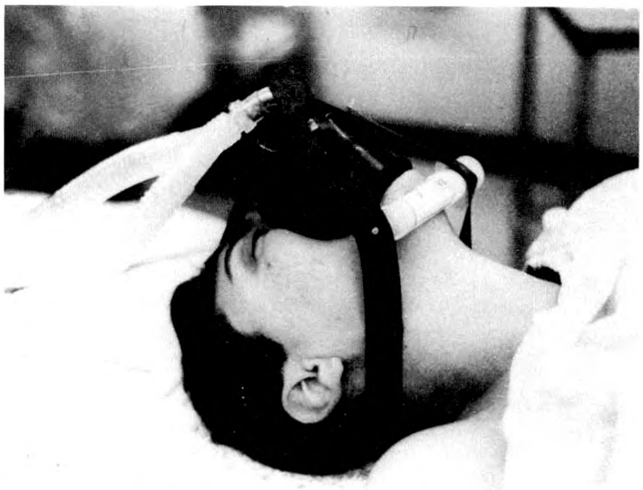

Figure 1. A 20-mL syringe provides chin support for a head harness with mask anesthesia.

A simple, self-supporting chin device is suggested using a 20-mL syringe as shown (Figure 1). For additional comfort, a piece of gauze can be placed between the syringe and chin. This device has a number of advantages. The nozzle of the syringe barrel and the fins of the plunger provide a convenient grip for the cervical straps of the harness. The bulky shape of the syringe acts as a fulcrum, elevating the straps well away from the mandible. This alters the momental forces in such a way that the system is self-supporting. Cervical straps may injure the marginal branch of the facial nerve (3), press on the facial artery, or impair venous drainage of the face and scalp by pressing on the internal jugular vein. The risk of these neurovascular injuries may be reduced using the syringe chin support, as the straps are elevated well away from these structures. Finally, syringes are cheap and readily available in different sizes. Suggested use is 20 mL for adults and 10 mL for adolescents.

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References

1. Evans PJD, McQuay HJ, Bullingham RES, LLoyd JW, Moore RA. Maintaining the airway. Was Guedel wrong? Inside or outside the mouth? Anaesthesia 1982;37:701–2.
2. Lyew MA. Mechanical airway maintenance. Can J Anaesth 1988;35:670–1.
3. Ananthanarayan C, Rolbin SH, Hew E. Facial paralysis following mask anaesthesia. Can J Anaesth 1988;35:102–3.

1990;71:714–7

Book Reviews

The Merck Manual of Diagnosis and Therapy, 15th ed., 3rd printing

Robert Berkow, ed. West Point, Pa.: Merck Sharp and Dohme Research Laboratories, 1989, 2696 pp, $25.00.

The Merck Manual of Geriatrics

William B. Abrams and Robert Berkow, eds. West Point, Pa.: Merck Sharp and Dohme Research Laboratories, 1990, 1267 pp, $20.00.

In 1899, a chemical manufacturing company published a slender manual of 262 pages designed to meet the needs of general practitioners selecting medications. Some 91 years later, that manual has evolved into a 2696-page text that has become a favorite among medical students for its portability and readability. The publishers are probably quite justified in their claim to be "the most widely used medical text in the world." With the steady aging of the population in the developed world and with the surge of new information in geriatrics, a separate text for geriatrics has emerged from Merck Sharp and Dohme.

The popularity of these two reasonably priced manuals lend them an importance beyond the font of information they contain. Because most medical students acquire at least one original *Merck Manual* early in their training, the Manual serves as an introduction to clinical medicine and the various specialties at a very impressionable point. It is very disappointing, therefore, that all references to anesthesia in these texts are written by specialists other than anesthesiologists. Although the editors invite suggestions and comments for revision, the very concept of having nonanesthesiologists writing about the speciality seems a bit strained.

For example, in the *Geriatrics Manual* section on surgery, the authors misstate the ASA classification and ascribe its use to assess risk, cite old data on perioperative myocardial infarction occurrence, and obliquely refer to the Goldman Criteria without mentioning them by name. Their knowledge of anesthetic agents and technique seem locked in the late 1970s or early 1980s with fentanyl apparently thought to be a nascent drug and methoxyflurane still in use.

The sections on pain control in both manuals are written by a neurologist, and the perspective on this multidisciplinary field is limited to that viewpoint. For example, intrathecal and epidural narcotics for postoperative pain relief are reported here to be mired in controversy, and the utility of patient-controlled analgesia in the elderly is dismissed as requiring too much manual dexterity. It is this reviewer's experience that elderly patients who have sustained hip fractures are quite capable of handling patient-controlled analgesia and that the introduction of spinal narcotics has been a giant step forward in the ability to provide pain relief.

Despite these faults with respect to anesthesia, the manuals are very well written and well edited, a considerable feat in view of the multitude of authors. The crisp prose is without the soporofic properties common to so many encyclopedic works. The table of contents and the index are two very important and necessary tools for navigating the facts presented and they serve the reader well. Although these manuals cannot be recommended for their anesthetic knowledge, they are still a handy resource for a quick refresher on subjects not encountered since medical school. It is to be hoped that the editors will update the anesthesia sections in future editions.

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Pain and the Sympathetic Nervous System, Current Management of Pain Series

Michael Stanton-Hicks, MD, ed. Boston: Kluwer Academic Publishers, 1990, 251 pp, $90.00.

Pain syndromes associated with sympathetic nervous system dysfunction are frequently seen by clinicians treating chronic pain. The most common syndrome, reflex sympathetic dystrophy (RSD), responds well to blockade of the sympathetic nervous system, and patients are commonly referred to anesthesiologists for treatment. Therefore, knowledge of the treatment of sympathetically maintained pain is important to anesthesiologists, whether they be in private practice or employed in multidisciplinary pain centers. A reference work for their use, devoted to sympathetically maintained pain, has long been needed.

This book is mostly directed toward the diagnosis and treatment of RSD. As a reference text on the subject, it is

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well organized and fairly comprehensive. Chapters on epidemiology, sympathetic nerve blocks, neurosurgical techniques, and the psychological aspects of RSD are complete and well written; these are highly recommended for any clinician who treats RSD.

The text does have a few flaws, however. The chapter on physiology and pathophysiology of the sympathetic nervous system, although well organized and well illustrated, is too long and goes into too much detail for a basic reference. Noninvasive treatment of sympathetically maintained pain is, on the other hand, very superficially reviewed. The chapter on intravenous regional sympathetic blocks is well written but lacks substantiation with references from peer-reviewed research. A large percentage of the references are review articles, chapters, or other articles unrelated to clinical research for the treatment of RSD. The chapter on peripheral nerve stimulation for treatment of causalgia is speculative and presents data and recommendations that have not previously been reported in peer-reviewed journals or substantiated by other authors. As such, the chapter presents interesting information that should not be incorporated in the general clinical treatment of RSD without further research. One last shortcoming of the book is its lack of a conclusive chapter to integrate the recommended treatment of RSD for the reader. Although methods are presented individually, the reader is left to conclude how each method should be incorporated into an overall treatment plan for the patient who presents with RSD.

The price of the book seems somewhat high, both in comparison to other books its size and to other books in the *Current Management of Pain* series. However, this text is one of only a few that can serve as references on the treatment of sympathetically maintained pain, and so it is recommended to physicians who treat this condition.

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Reflex Sympathetic Dystrophy, Current Management of Pain Series

M. Stanton-Hicks, W. Janig, and R. B. Boas, eds. Boston: Kluwer Academic Publishers, 1990, 210 pp, $59.95.

The publication of this monograph from the series *Current Management of Pain* closely followed the release of *Pain and the Sympathetic Nervous System*. This volume is based on the proceedings of a workshop on reflex sympathetic dystrophy (RSD) held in West Germany in 1988. Advertisements promise that this text will provide a "reference source" that will "serve as an invaluable manual for working with patients afflicted with this syndrome."

The editors have put together a very impressive table of contents divided into four sections. The first section covers general considerations in the diagnosis, incidence, epidemiology, and psychosomatic aspects of RSD; the second is devoted to basic research into the pathophysiology of the condition. The third section covers existing treatment of RSD, and the fourth covers new techniques of diagnosis and treatment. The only fault in the organization is that the chapter on peripheral nerve stimulator implantation for treatment of RSD should have been placed under "new techniques" because the technique is still unproven.

Unfortunately, the text does not live up to the excellence of the table of contents. All chapters are brief, superficial, and incomplete, and the quality of the writing is very uneven. In fact, the text resembles an unedited copy of abstracts from the meeting. Most of the authors from *Pain and the Sympathetic Nervous System* have chapters in *Reflex Sympathetic Dystrophy*. However, the chapters are significantly shortened. As an example, the chapter "Sympathetically Maintained Pain: Principles of Diagnosis and Therapy" is covered by the same author in 27 pages in the previous text and in only three pages in this book.

On a positive note, the chapters on basic research are very interesting, although many present preliminary research, opinion, and speculation. The authors review recent research and attempt to integrate the results into theories of spinal, neuropharmacologic, neurophysiologic, and peripheral bood-flow interactions in the pathophysiology of RSD.

In summary, *Reflex Sympathetic Dystrophy* does not fulfill its promise as a reference text on RSD and should not be purchased by clinicians with that intent, although it may be of interest to those involved in research and teaching. Clinicians will find *Pain and the Sympathetic Nervous System* to be a much more valuable resource.

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Anesthesia, 3rd ed.

R. D. Miller, ed. New York: Churchill Livingstone, 1990, 2420 pp plus 115 pp index in 2 volumes, $175.00.

Since 1980, Miller's *Anesthesia* has become the leading full-length textbook of anesthesia in the United States. The first edition was introduced as a comprehensive (but not encyclopedic), scholarly review of the state of our art, with each chapter complete in itself and redundancy encouraged to provide multiple points of view. The third edition's introduction acknowledges even more ambitious goals, the "best possible reference" and "the standard text for training programs," and points out several changes in the book.

The most evident changes are in the book's physical properties, some summarized in Table 1, along with those for Barash, Cullen, and Stoelting's *Clinical Anesthesia* for comparison. *Anesthesia* now comprises two volumes instead of three, with larger pages than before. The purchaser gets a lot of book for the money: 6.3 kg, 2.1 million words,

Table 1. Physical Properties of *Anesthesia* and *Clinical Anesthesia*

Physical properties	*Anesthesia* (Miller, 3rd ed.)	*Clinical Anesthesia* (Barash/Cullen/Stoelting)
Weight	6.27 kg	3.21 kg
No. of pages		
Text	2420	1515
Index	115 × 2	59
No. of words (estimated)	2.1 million	1.7 million
Page size (mm)	279 × 216 × .071	278 × 213 × .067
Typeface	Aster	Palatino
Size (points)	9	9
Spacing (points)	11	10
Fraction of page occupied by text	66%	70%
References	12,700	9,200
Price	$175	$99

and almost 13,000 references. The reviewer (with myopia and bifocals), as well as other readers, finds that Miller's book produces less eyestrain than does Barash, Cullen, and Stoelting's, which I can read for only 30 minutes at a time without rest. Both use 9-point type, but the line spacing is 11 points in *Anesthesia* and 10 points in *Clinical Anesthesia*. This, along with the wider margins and slightly less glossy paper, may account for the greater comfort one experiences when reading *Anesthesia*. The handsome new text is well laid out, with effective use of tables, charts, and diagrams.

There are new authors and chapters. These include individual chapters on pain management, monitored or "stand-by" care, various kinds of monitoring, hyperbaric medicine, pediatric cardiac anesthesia, anesthesia for orthopedic surgery, and measures to conserve blood. Two novel chapters are noteworthy. "The Management of General Anesthesia" deserves special attention from those who teach anesthesia, as its description of a simple general anesthetic also incorporates the teaching methods for which its author, Dr. Robert Willenkin, is well known. Also welcome is the chapter on "Teaching Anesthesia," which may present difficulties for those not familiar with the language of educators, but which has good advice for the many who teach anesthesia or who administer teaching programs. Despite the 80 chapters, one omission remains: major treatment of positioning in its own chapter.

How well does this new book fulfill the four goals of a major text? First, it may establish scholarly bench marks, assessing and delimiting our knowledge. This most ambitious goal was clearly foresworn for the first edition, but was possibly encompassed by this edition's ambition to be the best available reference. A comprehensive assessment of the scholarly merits of the entire book would require a dozen reviewers. The text remains uneven in the depth of its scholarship, although not as badly so as in the previous editions. A few chapters are relatively superficial, whereas many meet high academic standards.

Second, a major textbook provides a review for experienced readers. This form of continuing medical education receives little mention, perhaps because it does not involve travel for the participant or profit for speakers, but it has much to offer. *Anesthesia* easily fills this role. Some variation in style results from the number of authors involved. Nevertheless, perhaps because of the enhanced editorial review in this edition, all of the writing is at least readable and much of it is excellent. The material covered is up-to-date and the judgments offered not only are buttressed by contemporary references but are as well considered as one would expect from the authors and editors represented here. A regular program of rereading this book in its successive editions, as well as referring to it as clinical problems arise, would form the basis for an unsurpassed individual program in continuing medical education.

Third, textbooks serve as complete courses in anesthesiology. Such books must not only offer complete coverage but also keep in mind the neophyte reader, so that a first-year resident will need little help to learn from the text. *Anesthesia* is likely to perform well in this role. Basic sciences are well explained, beginning at an appropriate level and correlated with clinical material.

Fourth, a major text serves as a ready reference to answer questions that arise in the course of practice or teaching. In the introduction, Dr. Miller points out that special pains were taken in preparing the index, the 115 pages of which are duplicated at the back of both volumes. The convenience of this feature outweighs the necessary 4% increase in size, weight, and cost. Looking up 20 subjects that arose recently in teaching or clinical care, along with a few exotica meant to challenge the indexer, showed that the index is easy to use and almost always directs one to the relevant material. Subheadings are plentiful and rationally chosen. There were a few failings: the entry "masseter spasm" only referred to a brief paragraph in the chapter on muscle relaxants and neglected the much more complete discussion in the section on "malignant hyperthermia"; there was no entry for hair loss after anesthesia or management of patients with epidermolysis. The usefulness of a book this large, with this much redundancy in the coverage of various topics, depends heavily on the index. This index, along with the book's wide coverage and the extensive lists of references provided with each chapter, makes this text an excellent reference.

Comparison of this book with *Clinical Anesthesia* is inevitable, but neither is clearly superior; both are excellent. Most material is well covered in both books, but each offers chapters that are better than the corresponding ones in the other. For physical ease of reading and for the most recent publication date (by a year), choose *Anesthesia*; for a cheaper, lighter book in a single volume, choose *Clinical Anesthesia*. Though the prices seem high, the annual cost (1990 dollars) of maintaining current versions of both books at their current rates of revision is only $55, less than the cost of a night's lodging in a typical ASA convention city. Anyone who needs one of these books needs the other too, and this includes any resident, practitioner, or teacher of anesthesia.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Atkinson RS, Adams AD, eds. *Recent Advances in Anaesthesia and Analgesia.* Volume 16. New York: Churchill Livingstone, 1990, 215 pp, $38.00.

Campbell D, Spence AA. *Norris and Campbell's Anaesthetics, Resuscitation, and Intensive Care.* 7th ed. New York: Churchill Livingstone, 1990, 254 pp, $19.50.

Domino EF, ed. *Status of Ketamine in Anesthesiology.* Ann Arbor, Mich.: NPP Books, 1990, 583 pp, $95.00.

Freye E. *Cerebral Monitoring in the Operating Room and the Intensive Care Unit.* Developments in Critical Care Medicine and Anesthesiology, Volume 22. Boston: 1990, Kluwer Academic Publishers, 196 pp, $85.00.

Miller RD, Kirby RR, Ostheimer GW, Roizen MF, Stoelting RK. *The Year Book of Anesthesia 1990.* Chicago: C.V. Mosby, 1990, 364 pp, $54.95.

Saint-Maurice C, Steinberg OS, Armitage EN. *Regional Anesthesia in Children.* Norwalk, Conn.: Appleton & Lange, 1990, 200 pp, $70.00.

Spiess BD, ed. *Hemorrhagic Disorders.* Anesthesia Clinics of North America, Volume 8, Number 3. Philadelphia: W.B. Saunders Company, 1990, 189 pp, $69.00 annual subscription for four issues.

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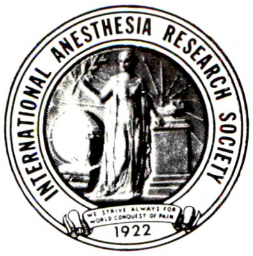

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
65th CONGRESS — March 8–12, 1991
Marriott Rivercenter • San Antonio, Texas

MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in December to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the **NEW IARS OFFICE ADDRESS:** Suite 140, 2 Summit Park Drive, Cleveland, OH 44131. Tel: (216) 642-1124.

MEETING SCHEDULE: **Registration:** Friday, March 8, 1–6 PM
Scientific Program: Saturday–Tuesday, March 12
Exhibits: Saturday–Monday, March 11

SCIENTIFIC PROGRAM

*T.H. Seldon Distinguished Lecture, Sunday, March 10, "**Anesthesiology and its Journals**"*
Nicholas M. Greene, MD, Emeritus Professor of Anesthesiology,
Yale University School of Medicine, New Haven, Connecticut,
and Editor-in-Chief, *ANESTHESIA and ANALGESIA*

REVIEW COURSE LECTURES:

MD Abel, MD — Transesophageal Echocardiography — Its Real Role in Clinical Anesthesia
PG Barash, MD — Preoperative Assessment of the Patient With Cardiac Disease
DR Bevan, MD, and RD Miller, MD — Anesthesia Literature — A Critical Approach to Reading and Writing
DR Cook, MD — Anesthetic Management of Neonatal and Infant Surgical Emergencies
MJ Cousins, MD — The Injury Response and the Prevention of Postoperative Pain
BG Covino, MD — New Techniques in Regional Anesthesia
N Ellison, MD — Blood Transfusions — When and What?
M Finster, MD — New Trends in Obstetric Pain Relief
AB Froese, MD — Ventilator-Related Lung Injury — New Concepts
TJ Gal, MD — Anesthesia and Gas Exchange — HPV, FRC, CC, and Other Acronyms
DE Longnecker, MD — The Case for Perioperative Blood Pressure Control
M Maze, MD — Alpha-2 Agonists and Anesthesia
SC Nicolson, MD — Perioperative Fluid Management in the Pediatric Patient
WS Nimmo, MD — Alternate Modes of Drug Delivery
GW Ostheimer, MD — Contemporary Issues in Obstetric Anesthesia
RG Pearl, MD — Sepsis — Etiology and Management
DS Prough, MD — Anesthetic Management of the Patient With Head Trauma
C Prys-Roberts, DM — Total Intravenous Anesthesia — Assessment of Adequacy
JG Reves, MD — Physiology of Cardiopulmonary Bypass
JJ Savarese, MD — Does the Choice of Muscle Relaxant Really Matter?
S Slogoff, MD — Outcome Studies in Anesthetic Data — A Perspective
NT Smith, MD — Perioperative Anesthetic Data — What to Do With It?
RK Stoelting, MD — Allergy and Anesthesia
JH Tinker, MD — How?/Should?/Does? Malpractice Litigation Affect Anesthetic Practice?
PF White, MD — Monitored Anesthesia Care — Appropriate Use of Adjuvant Drugs
MP Yeager, MD — The Role of Regional Anesthesia in Improving Surgical Outcome

PANELS

ANESTHESIA MACHINES AND VENTILATORS — Saturday AM, March 9
NW Lawson, MD, Moderator; JJ Andrews, MD, J Condurso, North American Drager, and JB Biondi, Ohmeda

YOU, THE ANESTHESIOLOGIST IN COURT — A MOCK MEDICAL MALPRACTICE TRIAL
(Based on an actual case) — Saturday PM, March 9
DH Morrow, MD, Moderator; Hon. D Hittner, F Stein, MD, TP Sartwelle, Esq., RJ Swift, Esq.

EMERGENCY AIRWAY MANAGEMENT — Monday AM, March 11
MS Gorback, MD, Moderator; JL Benumof, MD, EJ Krane, MD, CB Watson, MD

LEGISLATIVE UPDATE — LUNCHEON SESSION — Sunday, March 10
BP Stephenson, MD, and AC Lang, representing American Society of Anesthesiologists

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HOTELS: The Marriott Rivercenter will serve as headquarters hotel where all meetings and exhibits will be held. A limited number of additional rooms have been blocked at the St. Anthony. Reservation forms to be included in the December mailing must be used to obtain the discounted rates of IARS meeting registrants.

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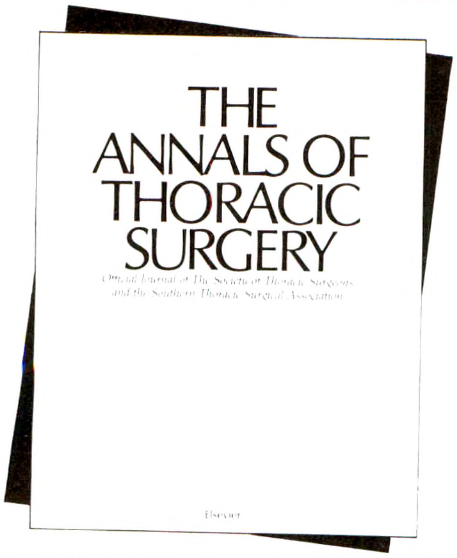

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Editor: **Thomas B. Ferguson, M.D.,**
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1990 Subscription Information, Vol. 49, 50 (12 issues)
ISSN 0003-4975
Personal Rate: $75.00* Institutional Rate: $116.00
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CHAIRPERSON, DEPARTMENT OF ANESTHESIOLOGY

The Medical College of Pennsylvania is seeking a physician to chair its Department of Anesthesiology who exhibits strong clinical academic leadership with a commitment to excellent patient care, teaching and clinical research. There should also be a clear commitment to the initiation of a residency program. The closing date for applications is January 1, 1991.

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424F/L

TENNESSEE
Anesthesiologist: Periodically full-time positions become available at the level of Instructor/Assistant Professor. Applicants must be board-certified or in the board process and be interested in resident teaching and clinical research. Tennessee license required. If you would be interested in having your name on file, please reply with curriculum vitae to John T. Chesney, MD, Interim Chairman, Department of Anesthesiology, University of Tennessee Medical Center at Knoxville, 1924 Alcoa Highway, Knoxville, TN 37920. UTMC is an Affirmative Action/Title IX/Section 504 Employer.

436F/L

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity/affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

446G/L

LOUISIANA
Anesthesiologist. Board-certified or -eligible anesthesiologist to fill clinical faculty positions at a University Medical Center. The position responsibilities include administration of anesthesia, teaching of residents, and supervision of CRNAs. Encouragement will be given to initiate or participate in research. Faculty rank and salary will be commensurate with experience. Louisiana State University Medical Center, School of Medicine in Shreveport is an affirmative action/equal opportunity employer. Send curriculum vitae to D. Richard Davis II, MD, Chairman, Department of Anesthesiology, LSU Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932.

468H/A

PACIFIC NORTHWEST
Position available for board certified or soon to be board certified anesthesiologist. Send CV and date available to Box 472H/A.

472H/A

CARDIOTHORACIC ANESTHESIA FELLOWSHIP
Washington University Medical Center. Applications are being accepted for 6- or 12-month fellowship (CA-4) starting in 1991. Full spectrum of adult cardiothoracic anesthesia including arrhythmia surgery, and active heart and lung transplantation program. Research opportunities are available. Address correspondence with CV and names of three references to Demetrios G. Lappas, MD, Director, Division of Cardiothoracic Anesthesia, Washington University Medical Center, 660 South Euclid Campus Box 8054, St. Louis, MO 63110.

483I/L

ANESTHESIOLOGIST
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496I/L

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497I/B

ILLINOIS
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511J/C

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO is recruiting for four faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol driven human studies. The three other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the four positions may be tenured track. Otherwise the positions are nontenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in Anesthesiology and a California Medical License is required. Possession of a certificate of special qualifications in Critical Care Medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego, is an Equal Opportunity/AA Employer. All applications received by December, 31, 1990 will receive thorough consideration.

518J/L

ATLANTA, GEORGIA: PAIN CONSULTANT
Position available for BC anesthesiologist pain consultant, Pain Management Services, Department of Anesthesiology in 500-bed acute-care hospital. Significant OR anesthesia required as well on a rotating basis. Applicant must have minimum of one year fellowship in pain and have experience in all aspects of acute, chronic, and cancer pain control including proficiency in neural blockade as applied to pain management. Replies with CV to Box 519J/L

519J/L

PEDIATRIC ANESTHESIA FELLOWSHIP

The Department of Anesthesiology, Columbia-Presbyterian Medical Center, is offering a fellowship in pediatric anesthesia at the Babies Hospital. The program is designed for individuals at the CA4, or CA3 and 4 level, who are interested in pursuing academic careers. Interested individuals should contact Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Babies Hospital, BN 440, 622 West 168th Street, New York, NY 10032.

520J/L

MISSOURI

Anesthesiologist, BE/BC needed to join hospital-based group practice in St. Louis area. CRNA supervision required. All specialties except open heart. Excellent salary and fringe benefits package. Send CV to Michael Stelmacki, 1 Insurance Center, Suite 101, Creve Coeur, MO 63141

521J/L

CALIFORNIA

From time to time faculty positions as an Assistant Professor become available in the *Regular Professorial Series (Tenure Track)* in the UCLA Department of Anesthesiology. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills; commitment to discovery; eligibility for a California Medical License; ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

526J/C

CALIFORNIA

Faculty positions in the *Clinician-Teacher* Academic Professorial Series in the UCLA Department of Anesthesiology are available. We are interested in all anesthesia subspecialties. Requisites include eligibility for a California Medical License and ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

527J/C

ANESTHESIOLOGISTS, MISSOURI

Anesthesiologists needed at assistant, associate, and professor levels. Must be board certified or board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri-Columbia Health Sciences Center. Interested applicants send Curriculum vitae to G.W.N. Eggers, Jr., MD, Professor and Chairman, Department of Anesthesiology, University of Missouri Health Sciences Center, Columbia, MO 65212.

529K/A

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY

The Department of Anesthesiology of Columbus Children's Hospital is expanding its fellowship program. Positions are currently available for a 1-year fellowship in pediatric anesthesiology. Children's Hospital of Columbus, Ohio is a 313-bed general pediatric institution with a surgery caseload of 13,000–14,000 cases per year. All pediatric surgical specialities are represented with large case loads in pediatric neurosurgery and cardiovascular surgery. Regional anesthesia in infants and children along with acute/chronic pain management experience is available. An active transplantation service is present. Opportunity for research is provided under the guidance of a full-time director of research. Inquiries should be submitted to J. David Martino, MD, Chairman, Department of Anesthesiology, Columbus Children's Hospital, Columbus, OH 43205.

531K/D

GEORGIA

BC/BE anesthesiologist needed to join private practice in the Atlanta area. Position available for July 1991. No hearts. Send CV to WS, 31 Hanarry Drive, Lawrenceville, GA 30245 or (404) 995-4680.

532K/D

CALIFORNIA

Anesthesiology, Pain Management Fellowship, UC Irvine. The University of California, Irvine, Department of Anesthesiology is accepting applications for CA4 fellowship positions in Pain Management. The rapidly expanding Pain Management Center at UC Irvine offers extensive clinical experience and education in all aspects of acute and chronic pain. With the addition of six new Pain Management faculty, there is extensive emphasis on the teaching of regional anesthetic techniques, invasive and noninvasive chronic pain regimens, and involvement of other disciplines. The clinic for chronic pain provides services to all types of pain patients, and the large University Medical Center is an excellent medium for the use of standard and sophisticated acute pain modalities. In addition to developing clinical expertise in pain management, our fellows get involved in research projects with the help of a full-time research assistant. Six-month or one-year fellowships are available. MD degree and California license are required. Send curriculum vitae and three references to Carl A. Hess, MD, Director, Pain Management Center, Department of Anesthesiology, University of California, Irvine, 101 City Drive South, Route 81A, Orange, CA 92668; (714) 634-6437. The University of California, Irvine is an equal opportunity employer.

541K/A

FELLOWSHIP—CARDIAC ANESTHESIA

The Department of Anesthesia, University of Toronto is accepting applications for a 12-month fellowship beginning January 1, 1991 or July 1, 1991. Experience and training will include all aspects of cardiac anesthesia, ICU, and/or clinical research for 2000 open heart patients per year. Candidates must have completed a recognized anesthesia training program and be eligible for academic licensure. Inquiries, CV, and three references should be addressed to Sallie J. Teasdale, MD, Director of Cardiac Anesthesia, The Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada, M5G 2C4.

542L/A

PAIN MANAGEMENT TRAINING AND PRACTICE

Looking for physicians interested in pain management. Graduates of pain fellowships and anesthesiology residencies are encouraged to apply. Will also consider and train physicians from other specialties who are interested in changing directions and going into the professionally and financially rewarding practice of pain management.

Training will be done in a busy, private practice, intervention-oriented pain management center, located in Dallas, Texas. The center emphasizes a wide variety of pain-relieving procedures with management of psychological and physical rehabilitation aspects in the patient's care. Attention will also be given to development of administrative knowledge in the management of a private pain practice. After training, physicians may be able to join our staff, or get our help and support in developing their own challenging and potentially lucrative pain management practices.

Training period may vary from 3 months to 1 year, depending on previous training. Compensation during training is highly competitive and after training it is potentially outstanding. Texas license is required. Please send CV to P.O. Box 802314, Dallas, TX 75380-2314; or call (214) 239-2190 for more information.

543L

MISSOURI

The Department of Anesthesiology of St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110–0250; telephone (314) 577-8750.

544L/D

ANESTHETIST

A vacancy exists for an anesthetist with FRCPC or eligibility for same, to join the academic staff of Memorial University of Newfoundland, Faculty of Medicine. The successful candidate must be eligible for licensure in Newfoundland.

Clinical responsibilities would be primarily at the General Hospital—Health Sciences Centre, which is the adult tertiary care center for the province of Newfoundland and Labrador. The Hospital has a well-developed multidisciplinary Intensive Care Unit and a Pain Clinic in which the Discipline of Anesthesia has a high profile. The Discipline of Anesthesia has a major interest in the University's newly established hyperbaric facility, which consists of a four-chamber diving complex (including a vertical wet chamber) rated at 1000 feet of seawater depth and capable of mixed gas saturation diving as well as hyperbaric oxygen therapy. An interest in research is essential; a special interest in hyperbaric medicine would be an advantage.

In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada. Write for further information to Henry J. Manson, MB, ChB, FFARCS, FRCPC, Professor and Chairman, Discipline of Anesthesia, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, Canada AIB 3V6.

545L

CRNA

Opening for CRNA in a 250-bed teaching medical center with significant trauma volume. Located 100 miles north of Los Angeles in an "All-American" city of 175,000, and close to many excellent recreational areas. Compensation and benefits are competitive. Quality of life exceptional. For more information, contact Human Resources, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305; (805) 326-2643, FAX (805) 326-2229.

546L/A

CHAIRPERSON—DEPARTMENT OF ANESTHESIA

Kern Medical Center seeks a Chairperson, Department of Anesthesia, who will form a corporation and independently contract for anesthesiologists' services to the Medical Center. The Corporation is to engage six (6) full-time anesthesiologists including the Chairperson. Kern Medical Center is a 240-bed teaching institution with a large emergent, OB and Neuro volume serving as a trauma center. Excellent quality of life is offered in an "All-American" city with a moderate cost of living, warm climate, and varied recreational activities.

Requires board certification, a California license, and five or more years of clinical practice experience. Chairperson will be eligible for a UCLA faculty appointment. Send resumes to Anesthesia Search Committee, Room C-150, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.

547L/B

ANESTHESIOLOGIST

Board eligible/certified anesthesiologists with California license to join group contracting services for Kern Medical Center, a busy teaching institution in growing area of 350,000 and an "All-American" city. If interested, submit resume to Search Committee, Room C150, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.

548L/B

NEW YORK: Fellowship—Neuroanesthesia

Clinician–investigator positions available for physicians who have completed their CA3 anesthesia year. Clinical responsibilities would include supervision and teaching of residents for a wide variety of neurosurgical cases, with special emphasis on cerebrovascular procedures. Research opportunities include a multidisciplinary program to investigate human cerebrovascular autoregulation using cerebral blood flow methodology both in and out of the operating room. Please send CV and names of three references to Edward D. Miller, Jr, MD, Professor and Chairman, Department of Anesthesiology, Columbia Presbyterian Medical Center, 622 West 168th Street, New York, NY 10032.

549L

RECRUITMENT FOR CERTIFIED REGISTERED NURSE ANESTHETIST (CRNA)

Rapidly expanding VA Medical Center in Dublin, Georgia is actively recruiting for a CRNA. Special salary rate of up to $63,901 is available to suitably qualified candidate. Benefits include generous salary, 5 weeks paid vacation, and 13 days earned sick leave per year, health plan, life insurance, federal retirement system and continuing education seminars. For further information, contact K. R. Varma, MD, chief of surgery, telephone (912) 272-1210, Ext. 215 or E. Gordon King, chief of staff, telephone (912) 272-1210, Ext. 202, VA Medical Center, Dublin, GA 31021. English language proficiency required for all direct patient care positions. An equal opportunity employer.

550L

YALE UNIVERSITY SCHOOL OF MEDICINE: Department of Anesthesiology

From time to time, faculty positions are available for both clinical anesthesiologists and research staff. These appointments are for immediate and future placement. Please respond before December 31, 1990 by sending your CV to Paul G. Barash, MD, Chairman, Department of Anesthesiology, Yale University School of Medicine, P.O. Box 3333, New Haven, CT 06510. Yale is an Affirmative Action Employer and provides equal opportunities for employment to all applicants.

551L

THE UNIVERSITY OF BRITISH COLUMBIA: Head, Department of Anaesthesia

The Faculty of Medicine, University of British Columbia invites applications and nominations for the position of Head of the Department of Anaesthesia. We seek an academic leader to be responsible for directing and developing the teaching and research programs of the department, which functions in seven teaching hospitals in Vancouver. The Department has four full-time and 103 clinical part-time faculty members. A candidate should hold a specialty qualification in anaesthesia and have a proven record of scholarly activity, extensive clinical experience, and a commitment to undergraduate and graduate medical education. Starting date will be July 1, 1991. Salary will be commensurate with experience and qualifications.

The University of British Columbia is committed to the Federal Government's employment equity program and encourages applications from all qualified individuals. In accordance with Canadian Immigration requirements, priority will be given to Canadian citizens and permanent residents. Applications, accompanied by a detailed curriculum vitae and the names of two individuals for references, should be directed by January 31, 1991 to Dr. M. J. Hollenberg, Dean, Faculty of Medicine, Room 317, Instructional Resources Centre, University of British Columbia, 2194 Health Sciences Mall, Vancouver, BC V6T 1W5, Canada.

553L

PENNSYLVANIA

Chairman of Anesthesiology. Northeastern Hospital of Philadelphia, a 231-bed acute-care community hospital, is seeking a board-certified anesthesiologist to accept the position as Chief of Anesthesia. This is an excellent opportunity for the successful candidate to build an aggressive department in a respected hospital performing approximately 7000 surgical cases a year. Northeastern has a progressive Department of Surgery and a hospital medical staff with a proven record of quality health care delivery. Interested candidates should send a resume to Lawrence Solish, MD, Chairman, Search Committee, Northeastern Hospital, 2301 East Allegheny Avenue, Philadelphia, PA 19134. Equal Opportunity Employer.

554L

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, DIRECTOR OF RESIDENT AFFAIRS
Faculty position available for board-certified/eligible anesthesiologist. Must have at least 5 years of postgraduate training, including research or other clinical training. As Director of Resident Affairs, incumbent will act as liaison between faculty and residents, and the Chairman in relation to all aspects of residency program. Incumbent will be responsible for the efficient running of the resident office and will be responsible for recruitment, education, and daily operation of the residency program. Under its umbrella, this position will also be responsible for medical students and postdoctoral fellows. Duties also include patient care, resident and medical student teaching, and research or specialized clinical activity. Special areas of interest may include any aspect of anesthesia. California medical license required. Send correspondence, curriculum vitae and list of professional references to Ronald D. Miller, Professor and Chairman, Department of Anesthesia, Box 0648, Room C-455, 521 Parnassus Avenue, University of California, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Employer.

555L/A

ANESTHESIOLOGIST(S)
The Department of Anesthesia, University of California, San Francisco, seeks candidates at the assistant or associate level(s) for teaching and clinical responsibilities at the Veterans Administration Hospital in San Francisco. Candidates must have training in clinical cardiovascular research. The ongoing research studies are multidisciplinary and multicenter, addressing perioperative ischemia and morbidity. The University of California is an Equal Opportunity Affirmative Action Employer. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, or, Dennis Mangano, MD, PhD, Professor, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648.

556L/A

MAINE
BC or BE MD to join group of three MD anesthesiologists and four CRNAs, in the practice of anesthesia, intensive care and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.

560L/E

BE/BC ANESTHESIOLOGIST
SW PA, 300-bed, modern community hospital to work with 3 MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to box 561L/B.

561L/B

PENNSYLVANIA
Anesthesiologist. Board-certified or board-eligible to join a five-member group providing CRNA supervised anesthesia. Community hospital, 90 minutes from Pittsburgh, with 11,000 cases per year, including open heart. Excellent fringe benefits, early partnership, cardiac or pain experience preferred. Reply to Box 562L.

562L

NEW YORK
CA 3 or 4 fellowship positions at Memorial Sloan-Kettering Cancer Center beginning July 1991. Straight clinical and clinician–investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic surgery. Send CV and summary of career goals to Mary E. Fischer MD, Director of Anesthesia Training, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

563L/B

DIRECTOR OB ANESTHESIA
Board-certified, 1-year OB fellowship, several years practice with administrative experience. Call (301) 365-7580. Write Director of Anesthesia, Columbia Hospital, 2425 L Street NW, Washington DC 20037.

565L/A

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383C/L

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505I/B

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335A/L

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473H/A

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552L/E

A WEEKEND OF PRACTICE ORAL EXAMS
Practice exams, not lectures. We are the original course in this format. 20 hours Category I CME credit, two board-certified instructors, 12 students maximum. Tampa, February 1–3 and March 1–3; Dallas, March 22–24; Denver, April 5–7. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480.

557L/A

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564L

ATRIC CARDIAC ANESTHESIOLOGIST

ı University (WVU) Health Sciences Center, Department of
gy, is recruiting for a pediatric cardiac anesthesiologist. Our
currently has 15 faculty members and sponsors an approved
ıining program, which has 24 residents.
ts for entry as Assistant Professor include completion of CA
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d a 60-bed rehabilitation hospital, now under construction.

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itional information contact: Edward Stullken, M.D., Chairman,
ient of Anesthesiology, WVU Health Sciences Center, Morgan-
VV 26506. Telephone: (304) 293-5411.

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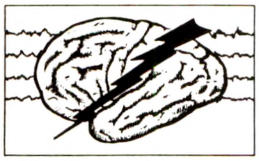

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complete information contact Mrs. Carolyn Schoenau, Pro-
n Coordinator, Anesthesiology Alumni Association of Flor-
Inc., Post Office Box 13417, Gainesville, Florida 32604 (Area
904 392-8959).

Stadol® *(butorphanol tartrate)*

For complete information consult official package circular.

INDICATIONS AND USAGE

Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS

Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS

Patients Physically Dependent on Narcotics

Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia

Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence

Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure

Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects

Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS

Certain Respiratory Conditions

Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function

Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery

Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication

Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy

The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human does.

Usage in Labor and Delivery

In general, the safety to the mother and fetus following the administration of Stadol during labor has been established, however, there have been a few reports of infant respiratory distress/apnea occurring after delivery (less than 1%; see Adverse Reactions). Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers

The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children

Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS

The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: Vomiting

Respiratory: slowing of respiration, shallow breathing, apnea

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE

Manifestations

Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment

The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY

Stadol (butorphanol tartrate Inj., USP) for I.M. or I.V. use is available as follows:
NDC 0015-5644-20 - 2 mg per mL, 2-mL vial
NDC 0015-5645-20 - 1 mg per mL, 1-mL vial
NDC 0015-5646-20 - 2 mg per mL, 1-mL vial
NDC 0015-5648-20 - 2 mg per mL, 10-mL multi-dose vial

For information on package sizes available, refer to the current price schedule.

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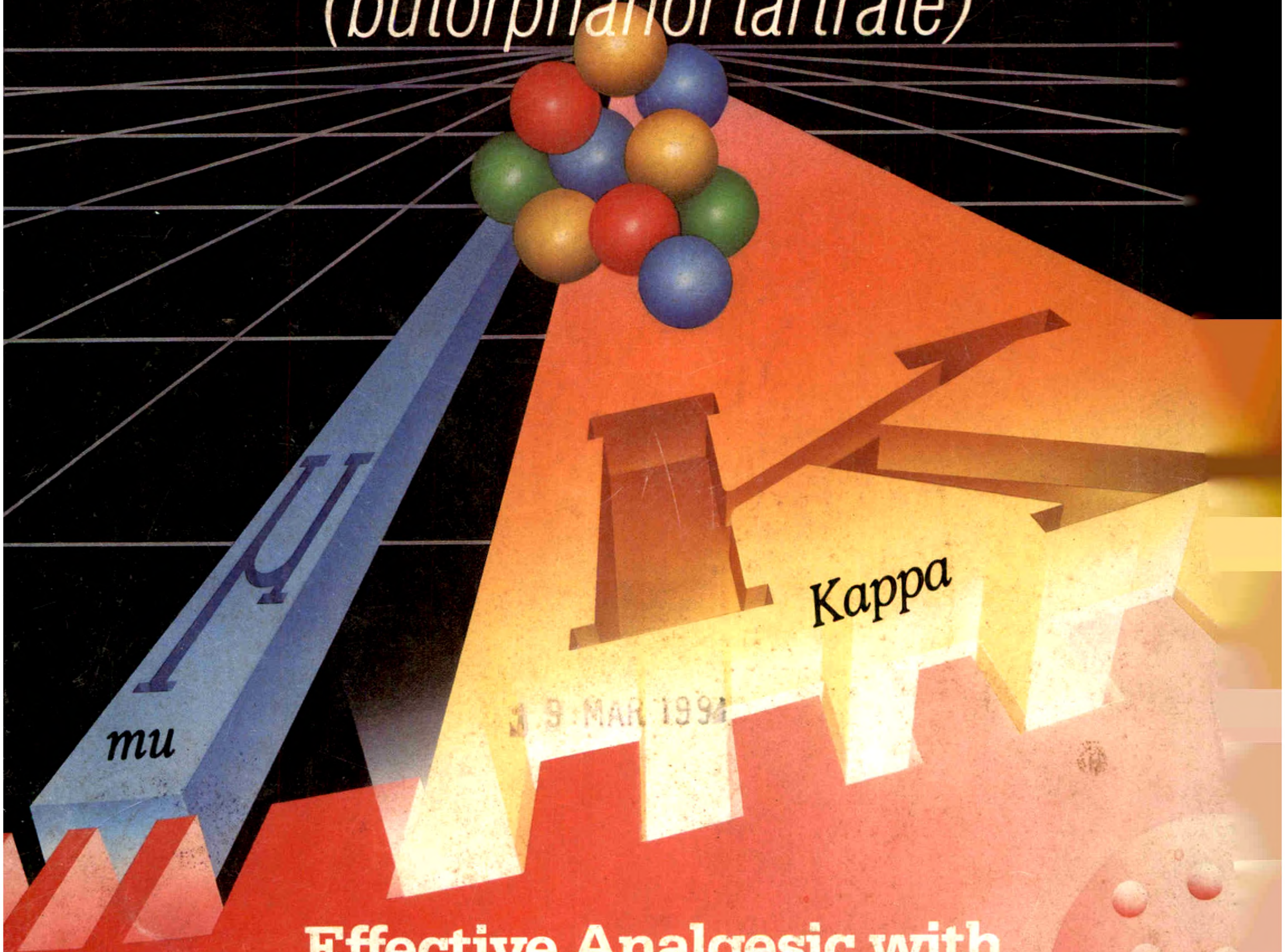

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Artist's interpretation of Stadol molecule interacting with *kappa* and *mu* opioid receptors.

See brief summary of prescribing information on next page.

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